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Review

Advances in the understanding of pathogenesis, and diagnostics and therapeutics for feline allergic asthma

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ABSTRACT

Asthma is a common inflammatory disease of the lower airways and is believed to be of allergic etiology in cats. As little progress has been made in establishing rigorous criteria to differentiate it from other inflammatory lower airway diseases such as chronic bronchitis, descriptions of 'asthma' in the literature have often been inaccurate, grouping this syndrome with other feline airway diseases. With the development of more sensitive and specific diagnostics, it will become easier to distinguish asthma as a disease entity. Pulmonary function testing with bronchoprovocation/bronchodilator responsiveness trials and biomarkers hold particular promise. Discrimination is of critical importance as targeted therapies for the allergic inflammatory cascade are developed and become available for therapeutic trials in pet cats.

Introduction

Asthma in humans is defined by the US National Heart Lung and Blood Institute[1] as a chronic disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and airway inflammation (Busse, 2007). Pet cats spontaneously develop a syndrome similar to human asthma and an understanding of the human disease has been relevant for an appreciation of the condition in cats (Reinero et al., 2009a). Species similarities have led to the development of feline models of allergic asthma for preclinical studies applicable both to feline and human health (Kirschvink et al., 2007a; Norris Reinero et al., 2004; Padrid et al., 1995b).

In pet cats, asthma is believed to be triggered by aeroallergens. Clinically the condition is associated with cough, wheeze and/or episodic expiratory respiratory distress. Although it is common, naturally occurring asthma in the cat is surprisingly poorly characterized. Previous studies that may have included cats with allergic asthma have used terms such as 'bronchial asthma', 'asthmatic bronchitis', 'allergic bronchitis', 'feline asthma syndrome', 'chronic bronchitis', 'chronic asthmatic bronchitis', 'chronic non-allergic bronchitis', 'chronic bronchitis with emphysema', 'idiopathic small airway disease', 'feline obstructive lung disease', 'feline bronchial disease (FBD)', 'feline chronic bronchial disease', 'feline chronic non-allergic bronchitis', 'feline lower airway disease (FLAD)', and 'feline chronic inflammatory lower airway disease'. This serves to underscore the current confusion about what comprises asthma versus other lower airway diseases in the cat (Adamama-Moraitou et al., 2004; Corcoran et al., 1995; Foster et al., 2004; Hirt et al., 2011; Mardell, 2007; Moise et al., 1989; Moriello et al., 2007).

These terms have been used with no clear consensus on how best to diagnose allergic asthma. Without the means to differentiate allergic asthma from other types of lower airway disease, there is a real potential for publishing misleading information. Understanding more about allergic vs. non-allergic inflammation in the airways will affect development of sensitive, specific and (ideally) minimally invasive diagnostics. Importantly, a definitive diagnosis of asthma is important for some aspects of environmental modulation (allergen avoidance), and for the design and evaluation of novel therapeutics targeting the allergic inflammatory cascade.

What causes asthma?

The major stimuli in humans which induce airway inflammation and airway hyperresponsiveness include pharmacological products (e.g., aspirin), environmental substances/air pollutants (e.g., ozone, environmental tobacco smoke), occupational factors (e.g., metals, animal and insect dusts, chemicals, etc.), exercise (especially but not exclusively in cold air), emotional stress, infections (in particular certain viruses), and allergens. In evaluating these risk factors in cats, there is little evidence that stimuli other than allergens are important driving forces behind most cases of asthma (see below).

Cats may develop an asthma-like syndrome after administration of potassium bromide, but this is rare, and rigorous documentation of airway inflammation and airway hyperreactivity was not performed in the study reported by Boothe et al. (2002). Ozone has

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been associated with airway hyperresponsiveness in cats, but has not yet been linked to eosinophilic airway inflammation (Takahashi et al., 1993; Takata et al., 1995). There are no specific reports associating occupational hazards with feline asthma, although with the closely shared environments of cats and humans, this is theoretically possible. Similarly no studies have been published on exercise triggering airway inflammation and airway hyperreactivity in cats; unlike dogs (sled dogs in particular), which model many features of cold exercise-induced asthma, cats are not winter athletes (Davis et al., 2002).

Emotional stress is thought to play an important role in the development of feline lower urinary tract disease/interstitial cystitis and other disorders but not specifically in asthma (Buffington, 2002; Buffington et al., 2006). One study in cats with idiopathic cystitis focusing on stress management by environmental modulation did report a significant decrease in signs referable to the lower respiratory tract but none of the cats had definitive documentation of asthma (Buffington et al., 2006).

The link between viral infections and asthma is complex, even in humans. Human epidemiological studies have suggested an inverse relationship between infection in early childhood and the development of asthma – the so-called 'hygiene hypothesis' (von Mutius, 2007). At one time, it was thought that early exposure to pathogens enhanced T helper cell 1 (Th1) immunity and polarized against Th2 immunity (the latter being the driving force behind allergic asthma). The term 'hygiene hypothesis' is now being refined to include early life exposure to a variety of commensal non-pathogenic organisms (Bjorksten, 2009). To add to the confusion, the site of infection may also be important with studies showing that upper respiratory tract infections are protective against the risk of asthma whilst lower respiratory tract infections increase the risk (Illi et al., 2001).

Early in life, kittens commonly develop upper respiratory tract infections with calicivirus and herpesvirus but no studies have examined the effect of these viruses on development of or protection against asthma. *Mycoplasma* spp. have been isolated from cats with eosinophilic and neutrophilic airway inflammation (Moise et al., 1989) but their role in the genesis of feline asthma is unknown. The single strongest identifiable underlying cause of asthma in humans is atopy, defined as the inherited predisposition to form IgE (Busse, 2007). It is likely, as in humans, that allergens are the most important stimuli for inducing asthma in cats.

Immunopathogenesis of allergic asthma

Inhalation of allergens leads to their uptake and processing by dendritic cells that sample antigens from the airway lumen. These allergens are processed and presented in conjunction with major histocompatibility complex class II (MHC II) to naïve Th0 cells in mucosal inductive sites below the epithelial surface. In susceptible individuals with the appropriate co-stimulatory factors, the resultant polarization to Th2-mediated immunity results in the production of cytokines which orchestrate the allergic inflammatory response and immunoglobulin (Ig)E production. High affinity FcεRI receptors on mast cells and basophils avidly bind IgE. Upon re-exposure to allergen, bound IgE is cross-linked leading to degranulation and further exacerbation of the inflammatory cascade. Ultimately, the patient develops hallmark features of asthma: eosinophilic airway inflammation, airway hyperresponsiveness/airflow obstruction and airway remodeling.

Evidence to support that asthma is allergic in cats

Increased incidence of human asthma in developed countries became apparent during the latter part of the 20th century, and there was a parallel increase in asthma incidence in cats in one urban setting (Ranivand and Otto, 2008; Redd, 2002). A major limitation of the feline study was that asthma diagnosis was confirmed by thoracic radiography (Ranivand and Otto, 2008), which is neither sensitive nor specific. However, the idea that shared environmental factors could be responsible for airway disease in both species is compelling (Reinero et al., 2009a).

In another study, the prevalence of physician-diagnosed atopic disease in over 4000 humans and their co-habiting pets with veterinarian-diagnosed allergic disease were compared (Schafer et al., 2008). The study concluded that the concomitant occurrence of allergic disease in humans and their pets was most likely to be due to shared environmental factors. Similar environmental allergens have been implicated in both humans and pet cats with asthma - including indoor allergens such as house dust mites and outdoor ones such as Bermuda grass allergen (BGA) (Adler et al., 1985; Busse, 2007; Kurata et al., 2002; Norris Reinero et al., 2004).

While compatible clinicopathological findings of asthma in conjunction with positive serum or skin test results for allergens are supportive of diagnosis, it is also recognized that the presence of allergen-specific IgE reactivity does not definitively imply that the allergens cause the disease. The next level of evidence was to use allergens identified in pet cats with spontaneously developing asthma and to test whether they could be used to reproduce an allergic asthmatic phenotype in research cats. Using either house dust mite or BGAs, the studied cats developed eosinophilic airway inflammation, allergen-specific hyperresponsiveness, a Th2 cell cytokine profile in blood and bronchoalveolar lavage fluid (BALF), induction of allergen-specific IgE, and airway remodeling (Norris Reinero et al., 2004).

One final piece of supportive information that asthma in cats is allergic in etiology is that allergen avoidance or allergen-specific immunotherapy (ASIT) have resulted in beneficial clinical responses in pet cats (Corcoran et al., 1995; Halliwell, 1997; Prost, 2008). Limitations of these studies included the fact that a diagnosis of allergic asthma was made solely by owners based on clinical respiratory signs (Halliwell, 1997), or by clinicopathological abnormalities where BAL results were normal or included neutrophilic inflammation (i.e., asthma and chronic bronchitis were likely lumped together) (Corcoran et al., 1995) or that efficacy of therapy was confirmed by remission of asthma symptoms without confirmation of improvement in airway inflammation (Corcoran et al., 1995; Prost, 2008). Moreover, concurrent therapy with corticosteroids and/or bronchodilators was allowed in one study during allergen-specific immunotherapy (Prost, 2008).

Previously it had been documented that 51% cats presenting for a re-evaluation of lower airway disease were 'doing well' without medication and only 49% required medication to control their clinical signs (Moise et al., 1989). With roughly half of the cats in that study showing improvement without medication, this supports the concept that clinical signs may wax and wane and are insensitive indicators of remission. Importantly, subclinical airway inflammation has been documented by repeat collection of BALF in cats with spontaneous asthma treated with high doses of oral glucocorticoids (C.R. Reinero, unpublished data) emphasizing the need for an objective means to assess resolution of airway inflammation.

Discriminating allergic asthma from other lower airway diseases: how is this done and why does it matter?

It is now believed that asthma and chronic bronchitis are the most common lower airway disorders in cats and should be considered as two distinct syndromes. Chronic bronchitis is thought to arise secondary to a previous insult (e.g., infection, inhaled irritants, etc.), which has permanently damaged the airways leading to many similar clinicopathological features of asthma. Diagnosis

of both disorders is made using a combination of clinical signs, thoracic radiography, exclusion of respiratory parasites, BALF cytology and response to empirical therapy with bronchodilators and glucocorticoids.

There is a tremendous overlap in these parameters, with some areas of discrimination. For example, only cats with asthma have intermittent expiratory respiratory distress resulting from bronchoconstriction. Cats with chronic bronchitis do not have spontaneous bronchoconstriction, although they may have airway hyperreactivity or fixed airflow limitation. Thoracic radiography is often not sensitive or specific for asthma or chronic bronchitis as it can be normal in up to 23% of cases (Adamama-Moraitou et al., 2004), and even when obvious radiographic lesions are present, there are diagnostic limitations based on the experience of the individual interpreting the radiographs (Gadbois et al., 2009). Nonetheless, while not specifically reported in cats, if radiographic evidence of hyperinflation is documented as transient (i.e., at least partly reversible with bronchodilators or after resolution of the acute and late phase IgE-mediated responses), that would support a diagnosis of asthma.

BALF cytology, with increased % eosinophils in asthma, remains a crucial diagnostic test to differentiate the condition from chronic bronchitis. Cats with chronic bronchitis have increased non-degenerative neutrophils in BALF. Of course, there is not always a clear cut distinction between asthma and chronic bronchitis, as chronic allergic airway inflammation may trigger damage leading to 'chronic asthmatic bronchitis' with mixed eosinophilic and neutrophilic inflammation (Moise et al., 1989). In other words, while BALF cytology is probably the 'gold standard' diagnostic for asthma in cats, it is not without flaws.

Additionally, there is still controversy on what constitutes 'normal' cellular percentages in feline BALF, with very wide ranges of eosinophil percentages (0–83%) reported in apparently healthy cats (Hawkins et al., 1990; McCarthy and Quinn, 1986, 1989; Padrid et al., 1991). It must be emphasized that a diagnosis of asthma is made by evaluation of the entire clinicopathological picture. The major diagnostic tool not yet widely available for pet cats, but tremendously useful in humans, is pulmonary function testing, which is a common, simple and non-invasive test. Spirometry allows for measurement of volume and flow of inhaled and exhaled breath to evaluate if airflow limitation is present. Bronchoprovocation testing using cholinergic agonists such as methacholine (Norris Reinero et al., 2004) or carbachol (Kirschvink et al., 2007a) can be used to assess airway reactivity in cats. More recently, bronchoprovocation using the indirect agonist adenosine 5′ monophosphate (AMP) has shown promise in cats to discriminate between those with and without airway inflammation, as the latter population would lack intermediate effector cells needed to trigger a response (Hirt et al., 2011).

A positive response to a bronchodilator is an important means by which to distinguish asthma from other disorders where airflow limitation is permanent (e.g., chronic bronchitis, chronic obstructive pulmonary disease); this is especially important since airway hyperreactivity can be a feature of other lower airway disorders and by itself is not specific for asthma.

Non-invasive pulmonary function testing, including tidal breathing flow-volume loops using a tight fitting face mask, forced expiratory flow-volume curves using a thoracic compression technique, or barometric whole body plethysmography (BWBP), have been used in cats to estimate airflow limitation (Bark et al., 2007; Hoffman et al., 1999; Kirschvink et al., 2007b; McKiernan et al., 1993). Recently there has been renewed interest in BWBP in cats, although results must be interpreted with caution since the index of airflow limitation measured by this technique called 'enhanced pause' (Penh) has been criticized for not reflecting pulmonary resistance as factors other than lower airway obstruction can impact Penh (Bates et al., 2004; Kirschvink, 2008).

More direct and accurate means for estimating airway resistance require anesthesia and may be invasive (Dye et al., 1996; Norris Reinero et al., 2004; Padrid et al., 1995b). They also require specialized training and dedicated equipment and are not routinely available for pet cats. Recent pilot studies using ventilator-acquired pulmonary mechanics have shown promise and the technique may become clinically useful given that ventilators are commonplace in many specialty practices and mechanics measurements from ventilators are comparatively easier than traditional methods (Lee-Fowler et al., 2009c; Rozanski et al., 2009).

Given the current limited availability to measure pulmonary function in pet cats and the invasive nature of collection of BALF, there is a strong need to develop minimally invasive testing to guide help differentiate asthma from chronic bronchitis and to monitor airway inflammation. Active areas of research in asthma include evaluation of biomarkers in blood, urine and exhaled breath condensate (Hoffmeyer et al., 2009; Murugan et al., 2009; Saude et al., 2009).

However, it is logical to ask why it is critical to discriminate between asthma and chronic bronchitis if they have similar and overlapping clinicopathological features and both respond to bronchodilators and glucocorticoids. The fundamental reason is that the two diseases differ in their underlying pathology, which is relevant for development of novel diagnostics and therapeutics. For example, biomarkers in blood, urine, BALF or exhaled breath condensate might be identified which can be used in the diagnosis, monitoring and prognostication of each disease individually. Attempts to do this in cats with asthma and chronic bronchitis have been unsuccessful to date mainly due to the relatively insensitive assays available (Nafe et al., 2010) but they still deserve further study. As another example, therapies specifically targeting allergic inflammation (e.g., allergen-specific immunotherapy, certain small molecule inhibitors, anti-IgE antibodies) would be useful only for asthmatic cats.

Other important differential diagnoses for asthma: lungworms and heartworm associated respiratory disease (HARD)

Other diseases may mimic the same clinical signs as asthma and have eosinophilic airway inflammation. Airway parasites (e.g., *Aelurostrongylus abstrusus*) can be tested for using fecal Baermann tests, may be found in BALF (Lacorcia et al., 2009), or can be ruled out by treatment with an appropriate anthelmintic (recommended). Heartworm associated respiratory disease complex (HARD) is a syndrome associated with death of immature L5 larvae that have reached the pulmonary arteries triggering an intense eosinophilic inflammatory reaction in both the pulmonary parenchyma and around the airways (Dillon et al., 2007). In cats not receiving selamectin (an avermectin antiparasitic agent used to prevent heartworm) a positive heartworm antibody test in the presence of clinical and pathological features of airway disease would support a diagnosis of HARD. It is unknown how long the eosinophilic inflammatory reaction persists in natural infections, but administration of selamectin can prevent reinfection with additional immature larvae.

Therapeutics

There is no single prospective, placebo-controlled study in pet cats with clearly defined asthma evaluating efficacy of glucocorticoids, bronchodilators or other treatments. Multiple retrospective studies in cats with spontaneous lower airway disease (asthma and chronic bronchitis) have documented some degree of beneficial clinical response to oral or parenteral glucocorticoids and/or bronchodilators (Adamama-Moraitou et al., 2004; Corcoran et al., 1995; Dye et al., 1996; Foster et al., 2004). Limitations of these

studies include small case numbers, differences in types and doses of drugs used, and insensitive means of monitoring response to treatment (i.e., there is a positive outcome based on clinical and radiographic improvement but with no documented improvement in airway inflammation or hyperreactivity).

In one study, antibiotics alone were used as treatment in a subpopulation of cats and half of the cats evaluated at a follow up had sufficient control of their clinical signs (Corcoran et al., 1995). As antibiotics do not affect allergic airway inflammation, we must ask whether the apparent response was due to secondary infection, waxing and waning of clinical signs, or a misdiagnosis? Before advocating a drug as effective for asthma in pet cats, more carefully controlled studies need to be performed. Experimental models of feline asthma are useful for this, where the number and types of sensitizing allergen and timing and dose of allergen exposure are controlled and serial diagnostics (BALF cytology and/or lung function testing) can be performed. While experimental models are intended to replicate the features of naturally developing asthma, it must be remembered that they are models of disease which may not accurately reflect all aspects of spontaneous asthma.

A prospective, randomized, placebo-controlled, crossover study in experimentally asthmatic cats confirmed that oral prednisone (10 mg/day) and inhaled flunisolide delivered though a spacer (500 μg/day) significantly decreased eosinophilic airway inflammation compared with placebo (Reinero et al., 2005). A subsequent study evaluating inhaled fluticasone showed no significant difference in the BALF % eosinophils when cats were given 44, 110 or 220 μg twice daily – all were equipotent in controlling airway inflammation (Cohn et al., 2010). Thus, as with humans receiving inhaled steroids, efficacy may plateau and giving more is not always better.

Bronchodilators reverse smooth muscle contraction mediated by specific allergen or non-specific irritants. However, given their lack of potent anti-inflammatory effects (some bronchodilators may have weak anti-inflammatory effects) they should not be used as monotherapy in asthmatics. This is because airway inflammation is a key event which further exacerbates airway hyperreactivity and remodeling and must be addressed directly (Busse, 2007).

Major classes of bronchodilators used in cats include methylxanthines, short- and long-acting beta-2 agonists (SABA and LABA, respectively), and anticholinergics. No feline studies have evaluated efficacy of methylxanthines on reversal of airflow limitation. The injectable SABA terbutaline (0.01 mg/kg) resulted in partial reversibility of airway obstruction in pet cats with lower airway disease using a direct measure of airway resistance (Dye et al., 1996). Metered dose inhalant delivery of the SABA albuterol (also called salbutamol) in pet cats with asthma at an unknown dose showed improvement in Penh (Rozanski and Hoffman, 1999). All other bronchodilators evaluated in asthmatic cats using some type of pulmonary function to assess changes in airflow limitation have been in experimental models using aerosol delivery.

Albuterol (100 μg), the LABA salmeterol (25 μg), the anticholinergic ipratropium (20 μg), and the combination of albuterol (100 μg) with ipratropium (20 μg) all delivered by metered dose inhaler (MDI), or albuterol (3.75 mg) or ipratropium (62.5 μg) by a nebulizer were tested for preventative effects against carbachol-induced bronchoconstriction using BWBP (Leemans et al., 2009a). Albuterol and ipratropium had a synergistic effect and salmeterol had the weakest degree of bronchoprotection. It was concluded that at the tested doses, delivery by MDI was as effective as by nebulization.

When albuterol (100 μg), ipratropium (20 μg) or albuterol (100 μg) with ipratropium (20 μg) were administered by MDI in experimentally asthmatic cats receiving allergen challenge (instead of non-specific bronchoprovocation with carbachol), results of testing by BWBP were unexpected but important (Leemans et al., 20010a). Compared with no treatment, none of the drugs significantly improved the time to recovery; in other words, the spontaneous resolution from allergen-induced early asthmatic reaction was not accelerated with these bronchodilators. This clearly has important clinical relevance as bronchodilators are the frontline medications for cats in *status asthmaticus*. Should we be recommending injectable bronchodilators in preference to inhaled bronchodilators as the delivery of the latter may be impaired in actively bronchoconstricting cats? Is the Penh a clinically useful parameter to reflect airway constriction or should time to recovery/time response curves be used? Or perhaps should we be investigating more sensitive and accurate indicators of airway resistance than BWBP before basing treatment recommendations on this type of mechanics? Additional studies need to be performed to answer these questions.

While SABA use in clinical practice is still considered the mainstay treatment for life-threatening bronchoconstriction, paradoxically, their overuse has been associated with increased risk of death in humans (Spitzer et al., 1992). The racemic form of inhalant albuterol is an equal mixture of an R-enantiomer and an S-enantiomer. The former possesses beneficial bronchodilatory properties and the latter possesses both bronchoconstrictive and pro-inflammatory properties (reviewed in Reinero et al., 2009b). After regular use, the S-enantiomer preferentially accumulates in the lung because of slower metabolism/clearance (Dhand et al., 1999) which enhances the negative bronchoconstrictive and pro-inflammatory effects, and prompts increased drug use resulting in a vicious cycle. With chronic use (twice daily for 2 weeks) in healthy cats, neutrophilic airway inflammation was induced de novo; in experimentally asthmatic cats, eosinophilic airway inflammation was exacerbated (Reinero et al., 2009b). This study supports the concept that inhaled albuterol should not be used as a regular part of the daily management of clinical signs of asthma.

Other drugs evaluated in experimental feline asthma include the antiserotonerigic drug cyproheptadine (speculated to have beneficial effects based on in vitro studies by Padrid et al., 1995a; 4 mg/day oral) and the cysteinyl leukotriene (cysLT) antagonist zafirlukast (20 mg/day oral), neither of which significantly reduced the % BALF eosinophils compared with placebo (Reinero et al., 2005). Glucocorticoids, cyproheptadine, and zafirlukast all failed to significantly alter airway hyperresponsiveness after methacholine challenge, perhaps due to the small number of cats in the study. The lack of effect of cysLT inhibition is in contrast to what was observed in a subpopulation of humans with allergic asthma, but compatible with prior feline studies documenting a lack of increase in the cysLT mediators after allergen challenge or blockade of the cysLT pathway failing to blunt ex vivo airway contractility in experimentally asthmatic animals (Norris et al., 2003; Padrid et al., 1995a).

It was uncertain whether the lack of effect of cyproheptadine was because the commonly used dose in cats was too low, as a pharmacokinetic study suggested a higher dose might be more appropriate in some cats (Norris et al., 1998). A later study examined the high dose of cyproheptadine (16 mg/day) and the second generation histamine 1 receptor antagonist cetirizine (10 mg/day) compared with placebo, and also found a lack of significant reduction in eosinophilic airway inflammation with either drug (Schooley et al., 2007).

The immunomodulator feG-COOH (a salivary tripeptide involved in neuroendocrine immunology) blunts allergen-induced airway inflammation in other animal models of asthma (Dery et al., 2001, 2004) and was evaluated in experimentally asthmatic cats. As proof of concept, a single dose of feG-COOH (1 mg/kg) was administered orally prior to allergen challenge and BALF was collected 24 h later. Compared with placebo, cats administered feG-COOH had significant reductions in airway eosinophilia, although the eosinophilic inflammation was only partially attenuated (DeClue et al., 2009). Since administration of feG-COOH prior

to allergen challenge is impractical in pet cats, a second study evaluating chronic administration of the immunomodulator was undertaken (Eberhardt et al., 2009). Interestingly, regular use of feG-COOH (1 mg/kg/day for 2 weeks) had no significant effects on eosinophilic airway inflammation or clinical signs compared with placebo. This is likely due to overlapping and redundant immunological pathways in chronic asthma that can override blockade of particular pathway(s) from chronic feG-COOH use.

Dietary consumption of omega-3 polyunsaturated fatty acids (ω3 PUFAs) have been investigated in experimentally asthmatic cats to blunt production of bioactive eicosanoids contributing to airway inflammation (Leemans et al., 2010b). The antioxidant luteolin was also added to the diet which was administered for 4 weeks. There was no significant difference in airway inflammation in treated vs. untreated asthmatic cats, but there was a reduction in airway hyperresponsiveness measured by BWBP. Whereas dietary supplementation with ω3 PUFAs and luteolin is clearly inadequate to treat asthma by itself, future studies could be undertaken to determine if it may be a useful adjunct, perhaps allowing for reduction in glucocorticoid dose.

All current treatments act relatively late in the allergic inflammatory cascade and are only palliative. To date, the only potentially curative therapy for any type of allergy is allergen-specific immunotherapy (ASIT). An abbreviated protocol for ASIT called rush immunotherapy (RIT) involves rapid loading of increasing doses of sensitizing allergen. The first protocol used in experimentally asthmatic cats involved alternating intranodal and subcutaneous allergen injections and led to significant reductions in airway eosinophilia, but was associated with (some severe) side effects (Reinero et al., 2006). Eliminating the intranodal injections improved safety, as did use of the adjuvant, CpG-ODN (Reinero et al., 2008). Because asthma is triggered by mucosally delivered allergens, a comparison of the safety and efficacy of mucosal vs. subcutaneous RIT protocols was performed (Lee-Fowler et al., 2009a). Whereas both protocols were associated with decreased eosinophilic airway inflammation and could be used, the subcutaneous protocol subjectively demonstrated more consistent resolution of clinical signs of bronchospasm after aerosol challenge with allergen.

A major challenge for use of ASIT in pet cats is the accurate identification of sensitizing allergens. Whilst it is straightforward to assess ASIT in experimental asthma because the sensitizing allergens are known, in pet cats allergenic triggers may be intermittent (e.g., seasonal) or their identification can be hampered by concurrent drug therapy. Additionally, identification of allergen-specific IgE does not necessarily imply that a particular allergen is causing asthma.

Intradermal skin testing (IDST) and serum allergen-specific IgE determination using an FcεRIα-based ELISA were compared in experimentally asthmatic cats (Lee-Fowler et al., 2009b). The results suggested that IDST might serve as a better screening test but either can be used to guide selection of allergens for ASIT. Importantly, this study also evaluated a different commercial laboratory for feline allergen-specific IgE determination and found the laboratory had unreliable results, including a failure to detect BGA-specific IgE as well as inappropriate identification of allergens to which the cats had not been sensitized. Future studies should be performed to evaluate more rigorously the accuracy of diagnostic laboratories offering allergen-specific IgE testing if ASIT is to become a viable treatment option for pet cats with allergic asthma.

Conclusions

There is evidence that asthma in cats is induced by an aberrant immune response to aeroallergens. Its distinct immunopathology lends itself to the design of novel diagnostics and therapeutics to discriminate it from other inflammatory airway diseases. Pulmonary function testing using bronchoprovocation and bronchodilator responsiveness is extremely useful in humans and further efforts to make this a practical test in cats need to be made. As current treatments are only palliative, the future challenge is to develop and test therapies which can reverse the aberrant immunopathology, perhaps by restoring normal immune 'tolerance' to allergens.

Conflict of interest statement

The author of this paper does not have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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