

The Cockroach and Allergic Diseases

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The cockroach represents one of the most common sources of indoor allergens worldwide, and 40%-60% of patients with asthma in urban and inner-city areas possess IgE antibodies to cockroach allergens. In Korean homes, four cockroach species have been found, of which the most commonly encountered is the German cockroach. The pathogenic mechanism underlying the association between cockroach allergens and allergic diseases has not been fully elucidated. Allergenicity is associated with the cockroach allergens themselves, enzymatic protease activity, and ligands for pattern recognition receptors. Although allergen-specific adaptive immune responses orchestrate the cockroach allergic response, recent data suggest that the innate immune system is also a critical contributor to pathogenesis. We review the current evidence for the demographics of cockroach exposure and sensitization, characteristics of cockroach allergens, and inflammatory responses to cockroach allergens initiated through protease-dependent pathways.

Key Words: Allergy; allergen; asthma; cockroach; protease-activated receptor 2

INTRODUCTION

Asthma, allergic rhinitis, and eczema have become the most common chronic diseases among children worldwide.^{1,2} Many researchers have indicated increases in the prevalence and economic burden of these diseases in the last few decades.^{3,4} It is largely accepted that gene-environment interactions are responsible for the development of asthma. In addition, because population genetic variability does not change with such rapidity, changing environmental factors are likely responsible for the increase in its prevalence. For nearly two decades, there has been mounting evidence that perennial allergens play a causative role in the development of asthma.^{5,6}

It is widely known that the cockroach is a source of inhalant allergens in allergic rhinitis and asthma. Bernton and Brown⁷ were the first to report positive skin tests to cockroach antigens in 44% of 755 allergy clinic patients in 1964. Kang et al.⁸ found a causal relationship between cockroach allergy and asthma following the inhalation of cockroach allergens by sensitized asthmatic patients. Subsequently, many studies have suggested that patients with asthma are commonly sensitized to this insect in several urban or inner cities around the world, including Seoul.⁹

This review describes the current evidence for the demographics of cockroach exposure and sensitization, characteristics of cockroach allergens, and inflammatory responses against cock-

roach allergens initiated through protease-dependent pathways.

PREVALENCE AND EPIDEMIOLOGY OF COCKROACH ALLERGY

Cockroach allergen levels have been associated with allergen sensitivity and asthma, particularly in urban environments.^{10,11} At least half of inner-city homes have clinically relevant levels of cockroach allergens.¹² As many as 30% of suburban, middle-class homes also have detectable levels of cockroach allergens; however, the levels in suburban homes are generally much lower than in inner-city homes.^{13,14} The National Cooperative Inner-City Asthma Study measured cockroach allergen Bla g 1 in dust that was collected from children's bedrooms and reported that 85.3% had detectable levels and 50.2% had high levels (>8 U/g).¹⁵ Subsequently, Eggleston et al.¹⁶ demonstrated that bedroom concentrations of Bla g 1 were related to cockroach allergen sensitization in children with asthma. In inner-

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city populations, 60%-80% of children with asthma are sensitized to cockroach allergens,^{16,17} and in one suburban population, the sensitization rate was 21%.¹³ A recent study measured cockroach allergens in the home environments of inner-city children in a population-based study and suggested a dose-response relationship between home Bla g 2 exposure and cockroach sensitization.¹⁸ Furthermore, Miller et al.¹⁹ suggested that prenatal exposure to cockroach and mouse allergens may prime the immune system of fetuses before birth and contribute to the development of allergies. Sensitization to cockroach allergens has been linked to the development of wheezing in young children.²⁰ Cockroach allergen levels have also been directly linked to poorer asthma outcomes in inner-city children with asthma, including increased asthma-related healthcare utilization.^{17,21} Kang²² also showed that inhalation of cockroach extract caused a significant decrease in lung function for asthmatic subjects with a cockroach allergy.

In a study of Korean homes, cockroaches were found in 62% of 174 homes.⁹ Four cockroach species, the German (*Blattella germanica*) (36.2%), American (*Periplaneta americana*) (33.3%), Japanese (*P. japonica*) (1.1%), and dusky brown (*P. fuliginosa*) (1.7%) cockroaches, have been found to infest homes in Seoul. Detached houses showed higher trapping rates than apartments. With respect to sensitization to cockroach allergens, we have previously shown 12.5% positivity using a skin test, placing it among the five most common allergens, including *Dermaphagoides farinae*, *D. pteronyssinus*, house dust, and *Alternaria* in children with allergic disease.²³ In a separate study, we also published that the positive rate of IgE levels specific to crude German cockroach extract in Korean children with atopic asthma was 18.7%.²⁴ Elevated levels of IgE specific for Bla g 1 and Bla g 2 were both found in 58.3% of those children. Additionally, we confirmed bronchial constriction in 6 out of 16 (37.5%) asthmatic children tested.²⁵ In another study of adolescents and adults with allergic diseases in 2003, the positive skin test rates to German and American cockroach allergens were 9.1% and 4.7%, respectively.²⁶ Recently, the cockroach infestation rates and sensitization rates might have decreased for city dwellers, given that the garbage disposal system has improved and insecticides are more commonly used in homes in Korea.²⁷

GERMAN COCKROACH ALLERGENS

Proteins derived from cockroach feces, saliva, eggs, and shed cuticles have been implicated as leading causes of allergic diseases, such as asthma.²⁸ The allergenicity of cockroach extract has been demonstrated in human subjects by means of skin tests, bronchial provocation tests, and radioallergosorbent tests (RASTs).²⁵ Immunoblot analyses have identified several allergenic components in German cockroach extracts with molecular weights of 12.5 to 110 kDa.²⁹ It is generally accepted that the major German cockroach allergens are Bla g 1 and Bla g 2. Pre-

Table. Characteristics of German cockroach allergens

Allergen	Biological action	Molecular weight (kDa)	IgE binding frequency (%)
Bla g 1	Midgut microvilli protein homologue	25-90	77
Bla g 2	Aspartic protease homologue (inactive)	36	60
Bla g 4	Lipocalin	21	40-60
Bla g 5	Glutathione <i>S</i> -transferase (Sigma class)	23	70
Bla g 6	Troponin C	17	50
Bla g 7	Tropomyosin	33	17
Bla g 8	Myosin light chain		

viously, we identified at least 15 IgE-binding protein bands in German cockroach extracts. Among them, proteins with molecular weights of 76, 64, 50, 38, and <14 kDa were the major German cockroach allergens.³⁰ Therefore, we suggested that Bla g 1 and Bla g 2 cannot be the sole indicators of German cockroach sensitization. Subsequently, several additional allergens, such as Bla g 4 (lipocalin or calycin), Bla g 5 (glutathione *S*-transferase [GST]), and Bla g 6 (troponin C) have been cloned, and their allergenicities have been studied.^{31,32} As compared with house dust mite (HDM) allergens, cockroach allergens have not been studied in detail. German cockroach allergens and their characteristics are summarized in Table.

Bla g 1 has an unusual structure consisting of a series of up to seven tandem repeats, each approximately 100 amino acid residues in length, and includes an allergen originally reported as Bla g bd90K.³³ It shows 37% sequence identity with midgut villi membrane protein from *Tenebrio molitor*,³⁴ but the biological function of cockroach group 1 allergen has not been elucidated.²⁷ Bla g 1 has a high IgE-binding frequency but weak intensity among Korean cockroach-sensitized subjects.³⁵ Measurement of Bla g 1 levels has been used to estimate exposure to cockroach allergens. Bla g 1 exposure above 2 U/g of dust is thought to be a strong risk factor for sensitization.¹⁶ Additionally, asthma symptoms occur with increased frequency with exposure to 8 U/g of dust or more among sensitized individuals.¹⁵

Bla g 2 is the most important cockroach allergen; the prevalence of sensitization to Bla g 2 is the highest among known cockroach allergens (54 to 71%).³⁶ Approximately 50% of serum samples from Korean patients who are sensitized to German cockroach antigens showed IgE reactivity to recombinant Bla g 2.³⁷ Bla g 2 has been found in cockroach gut tissues, raising the possibility that it may be a digestive enzyme.³³ Molecular cloning techniques determined the amino acid sequence of Bla g 2 and established that it is a 36-kDa protein that shares homology with a family of aspartate proteases.²⁵ However, amino acid substitutions in the catalytic triad of the molecule suggested that Bla g 2 is inactive as a protease. The determination of the crystal structure of Bla g 2 clearly showed amino acid substitutions in the catalytic triad and also identified it as a zinc-bind-

ing protein.³⁸ Its inactivity was confirmed using standard aspartate protease assays (milk-clotting and hemoglobin assays) in a recent study.³⁹ Cockroach allergens appear to be particularly effective at sensitizing atopic individuals. The proposed sensitizing threshold of Bla g 2 is 0.08 µg/g dust (2 U/g), whereas those of mite group 1 and cat allergens are 2 µg/g dust and 8 µg/g dust, respectively.⁴⁰

Bla g 4 is one of the most important German cockroach allergens, and a major IgE epitope of Bla g 4 has been identified at amino acid residues 118-152 near the C-terminus.³¹ Bla g 4 contains sequence diversity⁴¹; at least 10 isoforms of Bla g 4 were found to be produced by post-transcription modification, perhaps by RNA editing. Fan et al.⁴² also found that Bla g 4 is expressed only in the adult male reproductive system and that production of the allergen is stimulated by juvenile hormone.

GST was identified by immunoscreening of a *B. germanica* cDNA library using a serum pool from patients allergic to cockroach antigens and was designated Bla g 5.⁴³ Both natural and recombinant GST showed excellent IgE-binding reactivity and demonstrated positive reactions in intradermal skin tests among patients allergic to cockroach using as little as 3 pg of recombinant GST. GST was demonstrated to cause IgE responses in 70% of asthmatic patients allergic to cockroach antigens.⁴⁴ In two recent Korean studies, 20%-37.5% of IgE reactivity to Bla g 5 was reported.^{45,46}

A cDNA clone encoding troponin was obtained from the *B. germanica* cDNA library by IgE screening and was designated Bla g 6.⁴⁷ Its IgE-binding frequency was 50% among patients allergic to cockroach antigens. Recently, Un et al.⁴⁸ reported that 33%-45% of serum samples from Korean subjects recognized Bla g 6. Troponin is known to play an important role in muscle contraction as a calcium regulator.⁴⁹

Tropomyosin was cloned from the American cockroach and designated Per a 7. Purified tropomyosin could be recognized by 41% (12/29) of IgE-reacting sera.^{50,51} A cDNA sequence encoding the German cockroach tropomyosin, Bla g 7, was obtained, and its recombinant protein was produced.⁵² German cockroach tropomyosin has only minor sequence variations that do not seem to affect its allergenicity significantly.⁵³ Tropomyosins have been previously identified as important allergens in mites and shrimp. Arruda suggested that tropomyosin may be the basis for cross-reactivity among mites, cockroach, shrimp, and other invertebrates, and that the high degree of sequence identity has clinical significance.³³

INNATE IMMUNE RESPONSES AND COCKROACH ALLERGENS

Protease-activated receptors (PARs) are G protein-coupled 7-transmembrane domain receptors that can be activated by serine proteases via proteolytic cleavage.⁵⁴ Recent evidence suggests that the activation of PARs plays an important role in

inflammatory responses and immunological reactions.^{55,56} PARs are widely expressed in immune and inflammatory cells. Allergen-derived exogenous proteases, as well as endogenous proteases, can react with cell-surface PARs, which can then modulate the secretion of inflammatory mediators and further amplify the response. To date, four human PARs (PAR1-4) have been identified and cloned. PAR-1, -3, and -4 are activated by thrombin, and PAR-2 is activated by trypsin and tryptase.⁵⁴ PAR-2 can also be activated by a range of exogenous proteases, including some within important airborne allergens, such as HDM allergens.⁵⁷ Thus, PAR-2 has the potential to be involved in the pathogenesis of allergic response.

Recently, it has been suggested that allergic inflammation results not only from an exacerbated Th2-biased adaptive immune response, but is also heavily influenced by the direct activation of innate immune cells, such as bronchial epithelial cells, dendritic cells, and eosinophils, due to the allergens themselves and danger signals present in the allergen source.⁵⁸ Cockroach extracts have been shown to not only induce vascular endothelial growth factor (VEGF) production in bronchial airway epithelial cells *in vitro* and alter bronchial airway permeability,⁵⁹ but also trigger the release of pro-inflammatory cytokines, such as interleukin 8 (IL-8).^{60,61} Both events are largely dependent on the protease activity of cockroach extracts. Page et al.⁶⁰ reported that antibody-mediated blockade of PAR-2 cleavage inhibited IL-8 production induced by German cockroaches. In addition, we found that German cockroach extract protease activity induces IL-8 expression, which is transcriptionally regulated by nuclear factor-κB (NF-κB) and NF-IL6, coordinating with the extracellular signal-regulated protein kinase (ERK) pathway in human airway epithelial cells.⁶¹ We also reported that German cockroach extracts have a direct effect on human epithelial cells, in particular by generating [Ca²⁺]_i oscillations through Ca²⁺ release from thapsigargin-sensitive Ca²⁺ stores via the activation of PAR-2.⁶² Recently, we suggested that the synonymous c.621C>T polymorphism in PAR-2 is associated with the risk of atopy, potentially by altering PAR-2 gene expression.⁶³

Cockroach extracts also have a direct effect on human eosinophils, inducing degranulation, superoxide production, and increased surface expression of CD11b and CD69.⁶⁴ Wada et al.⁶⁵ has suggested that proteases from crude whole body extracts of German and Oriental cockroaches are important for the activation of PAR-2, degranulation, and superoxide and IL-8 production by human eosinophils.

CONCLUSIONS

The cockroach represents one of the most common sources of aeroallergens in Korea and around the world. Current evidence suggests that exposure to cockroach allergens is important in causing sensitization to these allergens. During allergic responses in the airway, it is clear that properties of the allergen dictate

features of the immune response and, therefore, the ensuing pathology. The complexity and diversity of cockroach allergens induce a multifaceted immune response involving both the innate and adaptive pathways of the immune system, which are activated by enzymatic protease activity and ligands for pattern recognition receptors at mucosal surfaces in the lung. Understanding and elucidating the roles of innate and adaptive responses in relation to cockroach allergen might lead to the development of new strategies for therapeutic intervention that will play a role in the future treatment of asthma and other allergic diseases.

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