

ORIGINAL ARTICLE

Rat-specific IgG and IgG₄ antibodies associated with inhibition of IgE–allergen complex binding in laboratory animal workers

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ABSTRACT

Objectives The relationship between exposure to rodent allergens and laboratory animal allergy is complex; at highest allergen exposures there is an attenuation of sensitisation and symptoms which are associated with increased levels of rat-specific immunoglobulin (Ig)G and IgG₄ antibodies. We set out to examine whether the increased levels of rat-specific IgG and IgG₄ antibodies that we have previously observed at high allergen exposure in our cohort of laboratory animal workers play a functional role through blockage of the binding of IgE–allergen complex binding to CD23 receptors on B cells.

Methods Cross-sectional survey of laboratory animal workers (n=776) in six UK pharmaceutical companies were surveyed. IgE–allergen complex binding to B cells was measured in 703 (97.9%) eligible employees; their exposure was categorised by either job group or number of rats handled daily.

Results We observed a significant decrease in IgE–allergen complex binding to B cells with increasing quartiles of both rat-specific IgG and IgG₄ antibodies (p<0.001). IgE–allergen complex binding to B cells was lower in workers with high allergen exposure, and significantly so (p=0.033) in the subgroup with highest exposures but no work-related chest symptoms.

Conclusions These findings demonstrate a functional role for rat-specific IgG/G₄ antibodies in laboratory animal workers, similar to that observed in patients treated with high dose immunotherapy who become clinically tolerant, suggesting a potential explanation for the attenuation of risk at highest allergen exposures.

BACKGROUND

Laboratory animal allergy is an important occupational health problem with a prevalence of specific sensitisation of around 15% and clinical allergy of about 10%.¹ The major determinant of laboratory animal allergy is exposure to rodent allergens but the exposure–response relationship appears to be complex since at highest exposures to rats, there is attenuation of both sensitisation and work-related symptoms.^{2–3} In a survey of animal workers in the UK pharmaceutical sector, we observed that the pattern of attenuation was associated with increased levels of rat-specific immunoglobulin (Ig)G and IgG₄ antibodies. In comparison with those producing rat-specific IgE only, the co-production of IgE and IgG₄ antibodies was associated with a twofold reduction in the risk of work-related chest

What this paper adds

- ▶ The role of allergen-specific immunoglobulin (Ig)G₄ antibodies at high allergen exposures in laboratory animal allergy is controversial with some studies suggesting a protective effect while others claim no protection against development of either sensitisation or symptoms.
- ▶ This study adds to the current knowledge by showing that high levels of rat-specific IgG and IgG₄ antibodies are associated with a significant decrease in IgE–allergen complex binding to B cells, suggesting a functional role for rat-specific IgG/G₄ antibodies in laboratory animal workers.
- ▶ These findings demonstrate a functional role for rat-specific IgG/G₄ antibodies in laboratory animal workers, similar to that observed in patients treated with high dose immunotherapy who become clinically tolerant, suggesting a potential explanation for the attenuation of risk at highest allergen exposures.

symptoms, suggesting that rat-specific IgG₄ antibodies may play a protective role in this setting.³

In support of our observation, a recent longitudinal study of laboratory animal workers observed a similar reduction in the risk of sensitisation at high allergen exposure with an associated trend of increased levels of mouse-specific IgG₄ antibodies,⁴ and an earlier study reported higher levels of specific IgG₄ antibodies in asymptomatic workers compared with those who had symptoms.⁵ In contrast, a survey of Dutch research workers found specific IgG₄ antibodies to be predictive of both prevalent and incident sensitisation or symptomatic allergy in atopic and rat-sensitised employees;⁶ in a similar population followed longitudinally, Krop *et al*⁷ reported that IgG₄ antibodies were not protective against either sensitisation or symptoms. A likely explanation for the differences observed within these longitudinal studies is the limitation that individuals often have previous exposure to laboratory animals at time of enrolment.

If it is true that specific IgG₄ antibody has a protective role then the question of mechanism arises. Patients who become clinically tolerant following

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high dose allergen immunotherapy with grass pollen have increased levels of specific IgG₄ antibodies that block IgE–allergen complex binding to CD23 receptors on B cells^{8 9} resulting in downregulation of both the T cell response and allergic symptoms.^{10 11} Indeed, measurement of the blocking of IgE–allergen complex binding to B cells is considered a better marker of clinical tolerance after discontinuation of immunotherapy than measurement of specific IgG₄ antibody levels.⁹ Evidence that specific IgG₄ antibodies have a similar functional role in the course of ‘natural’ immunity is currently restricted to bee keepers who following repeated bee stings during the summer season have detectable bee venom-specific IgG₄ antibodies that inhibit the binding of allergen–IgE complexes to CD23 receptors on B cells; this inhibition remains substantially elevated out of season.¹²

To date, there is no evidence for a functional role for specific IgG or IgG₄ antibodies in laboratory animal allergy. We hypothesised that laboratory animal workers with high allergen exposure develop a form of natural tolerance similar to that observed in patients treated with high dose immunotherapy who become clinically tolerant. To test this, we investigated whether the increased levels of rat-specific IgG and IgG₄ antibodies that we have previously observed³ play a functional role through blockage of the binding of IgE–allergen complex binding to CD23 receptors on B cells.

MATERIALS AND METHODS

Subjects

As previously described, in a cross-sectional study, we surveyed 776 employees of six UK pharmaceutical companies who were undergoing routine health surveillance for laboratory animal allergy.³ A total of 38 employees were excluded as they had less than a month’s contact with rats; a further 20 were excluded because we failed to collect complete exposure and/or clinical information from them. Of the remaining 718 employees, we had sufficient retained subject sera for the measurement of IgE–allergen complex binding to the CD23 receptor on B cells in 703 (98%).

The Royal Brompton Hospital/National Heart and Lung Institute ethics committee approved the study; written, informed consent was obtained from all participants (96-056 (95-001)).

Exposure and symptom assessment

All employees were invited to complete a questionnaire detailing their occupational exposure to rats.³ Employees were classified according either to the job they had ever had that incurred the highest exposure to rats—office or maintenance worker (low exposure), scientist (medium exposure), or animal technician or cage cleaner (high exposure)¹³—or to the maximum number of rats they had ever handled in 1 day (none, 1–10, 11–50, 50+).³ The questionnaire also enquired into eye/nasal and chest symptoms, the latter defined by wheezing, tightness of the chest or difficulty breathing. Symptoms were considered to be related to work if they occurred at work and/or improved when away from work.

Skin prick tests

We undertook skin prick tests with histamine (1%), saline, extracts of cat, grass pollen and *Dermatophagoides pteronyssinus* (50 000 SBU/mL, Allergopharma, Reinbek, Germany) and rat urinary protein (1 mg/mL, inhouse preparation).³ Atopy was defined by a positive (mean weal diameter of ≥ 3 mm greater than the response to saline) to one or more non-occupational allergens.

Measurement of rat-specific IgE

Rat-specific IgE to an extract of rat urine was measured using a radioallergosorbent test (RAST) as previously described.¹⁴ A 2% binding was chosen as the positive cut-off point, based on more than 25 years’ experience of using RAST in a wide variety of occupational allergens.

Measurement of rat-specific IgG and IgG₄ antibodies

Rat-specific IgG and IgG₄ antibodies were measured using an ELISA developed in our laboratory,³ and results are expressed as an optical density for each antibody measurement. Optical density values were divided into quartiles and values within the top quartile were considered positive (≥ 0.46 for IgG, ≥ 0.34 for IgG₄).

IgE–allergen complex binding to CD23 receptor on B cells

The IgE–allergen complex binding assay was performed and optimised as previously described.¹⁵ Briefly, the assay was carried out by incubating, for 1 h at 37°C, 10 μ L of indicator serum with 30 μ g/mL rat urine extract in the presence or absence of 10 μ L of sera. Complexes of rat-specific IgE antibody and rat urine extract were incubated with 100 000 EBV-transformed human B cells for 1 h on ice. Surface-bound IgE–allergen complexes on B cells were detected using a fluorescently labelled anti-IgE antibody and quantified using flow cytometry (FACSCalibur flow cytometer, Becton Dickinson, Franklin Lakes, New Jersey, USA). The data were expressed as the per cent relative binding to allergen–IgE complexes where binding with indicator serum alone is normalised to 100% using the following formula: % B cells bound to allergen–IgE complex = (% B cells bound using indicator and test serum / % B cells bound to allergen–IgE complex using indicator serum only) $\times$ 100.

Indicator serum was obtained by pooling serum from a panel of 23 individuals with high levels of rat-specific IgE antibodies; the same pool was used throughout this study. We established that 30 μ g/mL of rat urine was optimal for binding rat urine–IgE complexes by incubating four different sera with varying concentrations of rat urine (0–100 μ g/mL) (figure 1A). IgE dependency of allergen–IgE binding to B cells was assessed by heat-inactivating four different sera at 56°C for 30 min to specifically destroy IgE antibodies (figure 1B). IgE dose dependency was assessed by diluting four different sera (figure 1C) and B cells were pretreated with either with 0, 0.1, 1 and 10 μ g/mL unlabelled monoclonal antihuman CD23 or 10 μ g/mL matched isotype control for 1 h at 4°C to determine CD23 dependency and assessed using four different sera (figure 1D).

Statistical analyses

Analyses were restricted to the 703 laboratory animal workers who had a measurement of IgE–allergen complex binding to CD23 on B cells. Differences in the levels of allergen–IgE binding between groups of participants were compared using Student t tests and ANOVA. Where appropriate, Cuzick’s non-parametric test for trend was used. Some analyses were also restricted to those who had no work-related symptoms. All analyses were conducted using STATA V.11 (College Station, Texas, USA).

RESULTS

Characteristics of study population

The population had a mean age of 35.5 years; 52.8% were men and 43.7% atopic. The median (range) duration of laboratory animal exposure was 8.7 (0.1–41.6) years (table 1). The

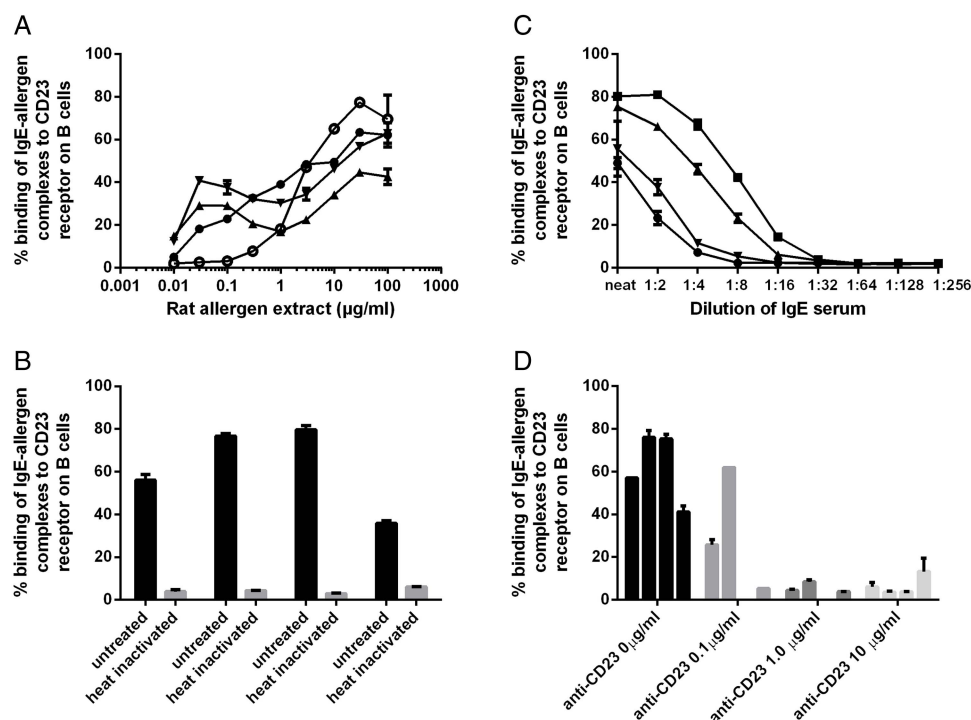


Figure 1 (A) Determine optimal allergen–IgE complexes binding to CD23 receptor on B cells, with varying concentration of rat urinary protein (0.01–100 μg/mL), in four individual sera with high levels of rat-specific IgE. (B) Determine IgE dependency of binding of allergen–IgE complexes to CD23 receptor on B cells as assessed by heat inactivation of four individual sera to destroy IgE antibodies. (C) Determine IgE dose dependency on binding of allergen–IgE complexes to CD23 receptor on B cells as assessed by dilution of four individual sera. (D) Determine CD23 receptor dependency on binding of allergen–IgE complexes to CD23 receptor on B cells as assessed by treatment of four individual sera with varying concentrations of anti-CD23 monoclonal antibody (0–10 mg/mL).

majority of employees (67.9%) were categorised as having medium exposure according to their job group; there was a broad distribution of the maximum number of rats handled per day (table 1).

Rat-specific IgE sensitisation was evident in 12.5% (skin prick test) and 12.9% (RAST) of employees. Upper respiratory, work-related symptoms were reported by 23.4% and lower respiratory, work-related symptoms by 8.2% of those surveyed; 7.7% had both upper and lower respiratory symptoms. The median (range) levels of rat-specific serum IgG and IgG₄ antibodies were 0.3 (0–1.7) and 0.1 (0–1.4), respectively. The majority of workers with rat-specific IgG and IgG₄ antibodies within the top quartile (considered ‘positive’) had no detectable rat-specific serum IgE antibodies (133/172, 77.3%).

Association between IgE–allergen complex binding to B cells and rat-specific, serum IgE, IgG and IgG₄ antibodies

There was a significant decrease in the binding of IgE–allergen complex binding to B cells in those employees with rat-specific IgG or IgG₄ antibody levels in the highest quartile compared with those in the lower quartiles ($p<0.001$ and $p<0.001$, respectively); in contrast, there was no significant difference between those with or without rat-specific IgE antibodies ($p=0.266$) (table 2). Furthermore, there was a significant trend for IgE–allergen complex binding to decrease with quartiles of increasing rat-specific IgG₄ ($p<0.001$) and IgG antibodies ($p<0.001$) (table 2).

Association between IgE–allergen complex binding to B cells and exposure to laboratory animals

Using either measure of laboratory animal exposure, there was lower IgE–allergen complex binding to B cells with increasing

exposure although the differences were not statistically significant (table 3). However, when the analysis was restricted to workers with no work-related chest symptoms, representing, perhaps, ‘the tolerant’ employees, we observed significantly less IgE–allergen binding to B cells in those with the highest exposure according to job category (table 4, $p=0.033$). No statistically significant trend across the four categories was evident ($p=0.143$) suggesting a ‘step-change’ at the highest exposure category only. Similar results were found when exposure was categorised by the maximum number of rats handled in a day (table 4).

DISCUSSION

Our findings demonstrate, for the first time in laboratory rat handlers, a relationship between IgE–allergen complex binding to B cells and increased levels of specific IgG and IgG₄ (but not IgE) antibodies. There was a significant trend for IgE–allergen complex binding to B cells to decrease with increasing quartiles of rat-specific IgG and IgG₄ antibodies. We observed lower IgE–allergen complex binding with high allergen exposure; this relationship appeared to be confined to those employees with no work-related chest symptoms, a group we suggest has developed clinical tolerance to exposure. The decreased binding of IgE–allergen complex to the low affinity IgE receptor (CD23) on B cells in the presence of rat-specific IgG and IgG₄ antibodies suggests a functional role for IgG antibodies, namely, the blocking of IgE–allergen complex from binding to B cells. This may be the explanation of the protective role for specific IgG₄ antibodies which we previously observed in this cohort, whereby the presence of serum-specific IgG₄ antibodies reflected a twofold reduction in the risk of developing work-related respiratory disease.³

Workplace

Table 1 Characteristics of study population

	Laboratory animal workers n (%) (n=703)
Age, mean (SD)	35.5 (9.7)
Male	371 (52.8)
Atopic	307 (43.7)
Work-related eye/nose symptoms	160 (23.4)
Work-related chest symptoms	56 (8.2)
Both symptoms	53 (7.7)
Either symptom	163 (23.7)
Employment duration, median (range) years	8.7 (0.1–41.6)
Highest exposed job group	
Low	84 (12.0)
Medium	477 (67.8)
High	142 (20.2)
Maximum number of rats handled per day	
0	119 (17.0)
1–10	164 (23.5)
11–50	157 (22.5)
50+	259 (37.0)
Sensitisation	
SPT rat +ve	88 (12.5)
Rat-specific IgE +ve*	91 (12.9)
Rat-specific IgE and IgG +ve	41/91 (52.6)
Rat-specific IgE and IgG ₄ +ve	39/91 (50.0)
Rat-specific IgE –ve	612 (87.1)
Rat-specific IgE –ve and IgG +ve	133/612 (21.8)
Rat-specific IgE –ve and IgG ₄ +ve	133/612 (21.8)
Rat-specific IgG +ve*	174 (25.3)
Rat-specific IgG ₄ +ve*	172 (25.0)
IgE–allergen complex binding (% binding), mean (SD)	111.1 (20.9)

*Measurements of IgE, IgG and IgG₄ only available in n=688.
SPT, skin prick test.

Such a protective mechanism has been well described in studies of immunotherapy in which tolerance is induced through immunisation with very high allergen doses. Our finding, using the same validated methodology,^{9 15} of a similar functional role for specific IgG₄ antibody in a ‘passive’ exposure setting is novel in that it appears to reflect the same mechanism arising from far lower levels of allergen exposure. Furthermore, the exposure route is different; high dose immunotherapy is delivered subcutaneously or sublingually whereas in laboratory workers the predominant route of exposure is by inhalation although an additional exposure via the skin from scratches and bites cannot be excluded. A recent study suggesting that natural tolerance in bee keepers, following frequent bee stings, is associated with a functional role for specific IgG₄ antibodies¹² may represent a similarly ‘natural’ form of immunotolerance although again the route of exposure is different and the dose of allergen may not be comparable with that of laboratory animal workers.

Specific IgG₄ antibodies are thought to play a role in tolerance by inhibiting the binding of IgE–allergen complexes to both low and high affinity IgE receptors (FcεRII and FcεRI, respectively) which leads to a reduction in both cellular responses, such as facilitated allergen binding⁹ and basophil histamine release,¹⁶ and allergic symptoms. It is likely that specific IgG₄ antibodies with increased blocking activity have higher avidity, either as a consequence of increased affinity to individual IgE epitopes or due to increased polyclonality;¹⁷ further

Table 2 Association between IgE–allergen complex binding to B cells and rat-specific IgE, IgG and IgG₄ antibodies

		IgE–allergen complex binding (%)			p Value
	n*	Mean	SD	95% CI	
IgE (% binding)					
+ve	78	108.7	20.9	104.0 to 113.4	0.266
–ve	610	111.5	20.7	109.8 to 113.1	
IgG (OD)					
+ve	174	106.1	24.4	102.4 to 109.7	<0.001
–ve	514	112.9	19.1	111.2 to 114.5	
IgG quartiles (OD)					
0–0.15	190	115.2	15.6	113.0 to 117.5	<0.001 p _{trend} <0.001
0.16–0.24	154	111.3	16.7	108.7 to 114.0	
0.25–0.45	170	111.7	23.9	108.1 to 115.3	
0.46–1.67	174	106.1	24.4	102.4 to 109.7	
IgG ₄ (OD)					
+ve	172	104.5	26.0	100.6 to 108.5	<0.001
–ve	516	113.4	18.1	111.8 to 114.9	
IgG ₄ quartiles (OD)					
0–0.02	178	116.5	14.3	114.4 to 118.6	<0.001 p _{trend} <0.001
0.03–0.10	173	112.3	18.5	109.5 to 115.1	
0.11–0.33	165	111.1	20.9	107.9 to 114.4	
0.34–1.43	172	104.5	26.0	100.6 to 108.5	

*Measurements of IgE, IgG and IgG₄ only available in n=688.
OD, optical density.

work is required to establish whether this occurs with high allergen exposures in laboratory animal workers.

Allergen-specific IgG₄ antibodies have been shown to account for at least a proportion of the inhibitory activity of IgE facilitated allergen binding in patients receiving grass pollen immunotherapy.^{8 9} The importance of ‘blocking antibodies’ was highlighted in a recent study with grass pollen immunotherapy, which demonstrated the parallel association between the serological inhibitory activity and clinical tolerance, despite levels of specific IgG₄ antibodies decreasing following withdrawal of immunotherapy.^{8 9} This suggests that the inhibitory bioactivity of specific IgG₄ antibody, rather than total specific immunoreactive antibodies, is more important for tolerance.

Our finding of what appears to be natural tolerance following exposure to laboratory animals is complimentary to that previously reported following high exposure in early life to cats in the home. Platts-Mills and colleagues¹⁸ have suggested that the

Table 3 Association between IgE–allergen complex binding to B cells and exposure

		IgE–allergen complex binding (%)			p Value
	n	mean	SD	95% CI	
Job exposure group					
Low	84	110.8	22.2	106.0 to 115.7	0.069
Medium	477	112.2	19.7	110.4 to 114.0	
High	142	107.6	23.6	103.7 to 111.5	
Maximum number of rats handled in 1 day					
0	119	111.2	20.9	107.4 to 114.9	
1–10	164	112.7	17.8	110.0 to 115.4	
11–50	157	113.8	20.3	110.6 to 117.0	
50+	259	108.6	23.0	105.8 to 111.4	

Table 4 Association between IgE–allergen complex binding to B cells and exposure in workers with no work-related chest symptoms

		IgE–allergen complex binding (%)			p Value
	n	Mean	SD	95% CI	
Job exposure group					
Low	75	112.1	19.9	107.5 to 116.7	0.033
Medium	421	112.4	19.9	110.4 to 114.3	
High	133	107.0	24.0	102.9 to 111.1	
Maximum number of rats handled in 1 day					
0	108	112.3	19.0	108.7 to 115.9	0.092
1–10	142	112.3	18.6	109.2 to 115.4	
11–50	139	113.7	20.1	109.2 to 117.1	
50+	237	108.6	23.4	105.6 to 111.6	

development of IgG and IgG₄ antibodies to cat allergen in the absence of IgE is associated with the absence of symptoms. They termed this response a ‘modified Th2 response’ (so called because both IgG₄ and IgE are dependent on the T helper type 2 cytokine interleukin 4).

We recognise several limitations in our study. The differences in IgE–allergen complex binding to B cells were small in comparison with those seen in immunotherapy studies. This is perhaps to be expected if we are observing a phenomenon of ‘natural’ or ‘passive’ tolerance; interestingly, similarly modest differences in IgE–allergen complex binding were seen in a comparison of bee venom allergic individuals (median 4.20) with tolerant bee keepers (median 0.02).¹² We did not undertake any IgG₄ depletion experiments to demonstrate that the decrease in IgE–allergen complex binding to B cells is due to specific IgG₄ because we had too little serum available; thus, we cannot determine whether most of the decreased binding with IgG antibodies is associated primarily with IgG₄ antibodies. Our exposure measurements were indirect but have been validated in previous studies.^{3 13}

In conclusion, we have demonstrated in laboratory animal workers a decrease in IgE–allergen complex binding to B cells, suggesting a functional role for rat-specific IgG₄ antibodies, which is reflective of the attenuation of specific IgE responses and increased production of specific IgG and IgG₄ antibodies at high allergen exposure. Further detailed observational studies are needed to enhance our understanding of passive tolerance to protein allergens.

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Contributors MJ acquired and interpreted data, wrote the manuscript and was involved in the conception and design of the study. HJ was involved in the conception, design of the study and writing the manuscript. SS analysed the data and was involved with writing the manuscript. JMH was involved with the analysis of data and design of the study. MHS was involved with acquiring the data. JNF was involved in the design of the study and acquiring and interpreting data. SRD critically revised the manuscript. PC was involved in the conception, design of the study and critically reviewed the manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval Royal Brompton Hospital/National Heart and Lung Institute (NHLI) ethics committee (96-056) (95-001).

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Data sharing statement There are no unpublished data from the study.

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