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Review paper

Bovine immunoglobulin E

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ABSTRACT

The recognition of homocytotropic antibodies and their occurrence in response to parasite infection preceded the recognition of IgE as a distinct antibody isotype in the bovine species. Passive cutaneous anaphylaxis was an early reliable and antigen specific method to detect IgE in bovine serum. Yet studies on the role of IgE in bovine disease awaited the production of polyclonal and monoclonal antisera specific for the bovine epsilon chain. Applications of antigen specific ELISA and Western blot techniques have demonstrated IgE responses not only to parasite antigens, but also to viral and bacterial pathogens. The role of IgE in vaccine enhanced disease and in eliciting anaphylactic responses to some vaccines has been elucidated using these immunological assays.

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1. Historical perspective

The definitive report identifying a new isotype of antibody (IgE) as the homocytotropic antibody responsible for type 1 hypersensitivity/anaphylactic activity was made in [Ishizaka and Ishizaka \(1967\)](#). Four years later [Hammer et al.](#) described in the bovine species a unique class of antibody that had characteristics similar to those of human

IgE. They showed that, like human IgE, the skin sensitizing ability was heat labile and that this activity could not be removed from serum by absorption with antisera specific for other bovine immunoglobulin heavy chains ([Hammer et al., 1971](#)). The antibody class responsible for the passive cutaneous anaphylaxis reaction (PCA) in cattle was independently characterized by [Wells and Eyre \(1972a,b\)](#) and shown to be analogous to the newly described IgE isotype. In a German publication antibodies responsible for anaphylaxis were demonstrated by passive transfer to colostrum deprived calves ([von Bentein et al., 1976](#)).

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In 1997 the bovine immunoglobulin E epsilon chain was sequenced by Mousavi et al. (1997). The homology with sheep epsilon chain was 87%; and it was lower with dog (62%), horse (58%), primate (55%), and mouse/rat (52%). The high homology with sheep is not surprising and accounts for our earlier success in performance of PCA with bovine IgE on sheep skin (Gershwin, 1981).

2. Methods of IgE detection and quantitation

Despite the early progress in identification of bovine IgE, production of antisera for use in its detection took many more years. Early studies on bovine IgE utilized the passive cutaneous anaphylaxis test (PCA) to identify and measure IgE activity; these antibodies were often referred to as homocytotropic antibodies. Development of antisera specific for human IgE was aided by the early recognition of an IgE myeloma (Stanworth et al., 1967). The unavailability of a myeloma protein in cattle meant that purification of IgE from bovine serum containing nanogram amounts was required for development of antisera. The first polyclonal antiserum for bovine IgE was reported in 1977 (Nielsen and Wilkie, 1977). A few years later our group produced a polyclonal anti-bovine IgE reagent using standard gel chromatography to purify IgE from cows immunized with ovalbumin in alum or incomplete Freund's adjuvant. Detection of IgE in fractions from gel filtration columns was accomplished by performing passive cutaneous anaphylaxis (PCA) tests on calf skin. In the course of this work other species were tested as potential PCA recipients and only goat and sheep were capable of being sensitized by bovine IgE (Gershwin, 1981). This antibody was used in an ELISA to measure initially total IgE and later antigen specific IgE (Gershwin and Dygert, 1983). Polyclonal antiserum was also produced against bovine IgE by Barratt et al. (1985) who used this reagent to study hypersensitivity to dietary components in young calves.

In one application of our polyclonal anti-bovine IgE reagent immunohistochemical detection of bovine IgE containing cells was performed on frozen sections from a variety of tissues that were taken from an experiment in which calves received either aerosolized ovalbumin or *Micropolyspora faeni* (recently renamed *Saccharopolyspora rectivirgula*) antigen over a 9-week period. Frozen sections were stained with anti-IgE followed by conjugate and substrate. Image analysis was used to enumerate percent of cells that were positive for IgE. The greatest concentration of IgE positive cells was in the retropharyngeal and bronchial lymph nodes from calves that had received aerosolized OA; while control calves immunized by the parenteral route had the greatest concentration of IgE positive cells in the spleen. This study was the first to show distribution of IgE containing cells in secondary lymphoid organs in the bovine species (Gershwin and Olsen, 1985).

Production of monoclonal antibodies specific for bovine IgE was accomplished in 1988. (Thatcher and Gershwin, 1988). Mice used as splenocyte donors were immunized with semi-purified serum derived bovine IgE. The resulting eight hybridoma clones were all positive on reverse cutaneous anaphylaxis and all could be used as sensitizing antibody for total IgE sandwich ELISA. One clone (E5) was

useful in immunohistochemistry, Western blot, and antigen specific ELISA. This latter antibody has been extensively used and shared over the past 20 years. Using the monoclonal antibody in an assay for total IgE, colostral transfer of IgE was demonstrated in calves (Thatcher and Gershwin, 1989a).

3. IgE responses to parasite antigens

Early associations of IgE with gastrointestinal parasite infection were made using the PCA test; as reported for *Fasciola hepatica* (Doyle, 1973). The protective role of IgE in defense against parasites is well recognized. Measurements of total IgE, using a standard serum pool, in calves before and after exposure to parasite contaminated pasture showed a marked increase in IgE level after exposure (Gershwin and Dygert, 1983; Thatcher et al., 1989b). Later using a modified form of the same assay system Miller et al compared total IgE levels in four groups of parasite naïve calves: barn housed uninfected, barn housed experimentally infected, clean pasture housed, and contaminated pasture housed. Results showed that the calves housed on contaminated pasture had a significantly greater total IgE serum level than any of the other groups (Miller et al., 1996).

Baker and Gershwin examined total and *Ostertagia*-specific IgE in serum collected monthly from cows, calves, and yearling heifers of several beef breeds. A seasonal pattern of total and *Ostertagia*-specific IgE was evident: both levels were highest in the spring. In addition, there was a breed effect, with the Angus-cross cattle showing higher IgE levels than the other breeds tested. Estimates of *Ostertagia* infestation, based on fecal egg counts, paralleled IgE levels (Baker and Gershwin, 1992). In a subsequent study in which Holstein calves had surgically placed cannulas in the abomasal efferent lymphatic vessel, serum and abomasal lymph were evaluated for total and *Ostertagia*-specific IgE. Calves were grouped into six groups with exposure protocols designed to approximate either type 1 *Ostertagiosis*, type 2 *Ostertagiosis*, or a mixture of types 1 and 2. Abomasal parasites were recovered at necropsy and classified into adult and immature forms; and numbers were compared with IgE levels. Serum proved to be less useful than lymph in predicting worm burdens. Total IgE in lymph correlated inversely with numbers of fourth stage larvae and late fourth/fifth stage larvae. Interestingly (and in contrast to the previous study) there was an inverse correlation between *Ostertagia*-specific IgE and numbers of adult *Ostertagia*. Sequestration of IgE in animals with heavy infestations may account for these observations (Baker and Gershwin, 1993).

A field study of nematode resistance in Nelore-breed cattle was conducted in Brazil (Bricarello et al., 2007). In this study the predominant nematodes were *Cooperia* and *Haemonchus*. In the 100 weaned male cattle a resistant and a susceptible group were identified based on fecal egg counts. The resistant group had significantly higher total serum IgE levels and higher mean eosinophil counts than the susceptible group, prompting the authors to conclude that total IgE levels might serve as a marker to identify

resistant and susceptible cattle. The IgE ELISA used in this study was performed using a monoclonal antibody specific for ovine IgE. In another study the same antibody was used to evaluate IgE responses to lungworm (*Dictyocaulus viviparus*) in calves. Protection correlated with total IgE levels and parasite specific IgE was demonstrated in serum by Western blot (Kooyman et al., 2002).

The relationship between tick (*Rhipicephalus appendiculatus*) resistant and susceptible cattle and IgE responses was demonstrated using the PCA test (Binta et al., 1984). Serum from tick resistant cattle sensitized skin of naïve recipients for PCA; while serum from tick sensitive cattle failed to do so. Heat inactivation proved that the responsible antibody was IgE. In another study relationships between total IgE levels, ecto and endo parasitism, and BoLA antigens were examined. In 80 cattle there was only one BoLA antigen that had a significant effect on IgE levels (W20). Cattle expressing this antigen had lower levels of IgE than cattle that lacked the W20 antigen. Cattle with high IgE levels had high *O. radiatum* egg counts, a nearly significant observation, $p = 0.07$ (Stear et al., 1990).

4. IgE responses to aerosolized antigens

Unlike humans and cats cattle do not develop naturally occurring asthma. It is tempting to speculate that the intensive exposure to bacterial LPS in the barn/feedlot environment enhances a T helper cell type 1 immune response thereby fulfilling the “Hygiene Hypothesis” (Renz et al., 2006). Nonetheless cattle can and do develop IgE antibodies after antigen exposure by aerosol administration. We evaluated the IgE response to inhaled ovalbumin (OA) in serum and during a 9-week course of 3–5 aerosol exposures to 1% OA per week. Passive cutaneous anaphylaxis (PCA) testing performed on sera showed positive reactivity with serum for the parenterally immunized control but not for the OA aerosolized only calves. In contrast, direct OA ELISA indicated positive reactivity for two of three calves that received aerosol (Gershwin and Olsen, 1984a,b). More recently, we found that calves exposed to OA aerosol during the first 6 days of an infection with bovine respiratory syncytial virus (BRSV) responded with significantly greater levels of OA specific IgE in pulmonary efferent lymph than uninfected controls (Gershwin et al., in press).

The IgE response to aerosolized *M. faeni* (recently renamed *S. rectivirgula*), the causative agent of bovine farmer’s lung disease, was examined by Wilkie after parenteral immunization and by aerosol exposure. Calves in that study showed a hyperpnea after aerosol challenge (Wilkie, 1976). Our group also studied IgE responses to *M. faeni* alone and in association with BRSV infection. In two of three calves exposed for 9 weeks to aerosolized *M. faeni* there was a substantial specific IgE response demonstrated by ELISA (Gershwin and Olsen, 1984a,b). Hyperpnea was not a clinical feature in these calves. In subsequent studies we showed that BRSV infection and *M. faeni* aerosol exposure enhanced lung pathology and increased IgE responses to both organisms (Gershwin et al., 1990, 1994).

5. IgE responses in viral infection

The demonstrated correlation between severity of disease in human infants infected with respiratory syncytial virus (RSV) and RSV specific IgE levels in serum and secretions prompted our group to examine the possibility that calves infected with BRSV might also be making IgE specific for viral proteins. Further evidence for this hypothesis consisted of field observations of anaphylactic responses to BRSV vaccination. Thus, we developed a BRSV IgE specific ELISA and applied it to BRSV infection studies (Stewart and Gershwin, 1989a,b). In these experiments we found that BRSV specific IgE correlates with clinical severity of disease. Subsequently we utilized a lung lymph cannulation technique to study BRSV specific IgE in efferent lung lymph. Again, IgE levels were shown to correlate with clinical severity. Moreover, cytokines IL-4, IFN- γ , and IL-2 were semi-quantified by RT-PCR on RNA from lung lymph pellets. While IL-4 was primarily present during the first 4 days of infection, both IL-2 and IFN γ were present during the 10 days course of infection (Gershwin et al., 2000).

The role of BRSV specific IgE in vaccine induced disease enhancement is discussed under vaccine associated IgE responses.

There has been speculation that IgE responses mediate the skin lesions seen in cattle infected with bluetongue virus (BTV). Anderson et al examined this hypothesis and showed a correlation between clinical dermatitis/stomatitis and BTV specific IgE, while a second study did not show such a correlation (Anderson et al., 1987; Odeón et al., 1999).

6. IgE responses to bacteria

Studies by our group using ELISA and Western blot analysis of serum from normal dairy cows showed that a low level of IgE antibodies reactive with *M. hemolytica* was present in serum of some asymptomatic cows, even though vaccination of calves with a commercial *M. hemolytica* bacterin failed to induce an IgE response (Gershwin and Frieberthauser, 1987). Many of these calves were nasal culture positive for *M. hemolytica* and thus had chronic low grade mucosal stimulation. McBride et al infused lungs of calves with *M. hemolytica* and measured IgE (as well as other isotypes) in serum and lung lavage secretions. They found in all of the inoculated calves that IgE was present 1–2 days after inoculation (McBride et al., 1992). Such a rapid response would be possible if priming had already occurred as predicted by our earlier observations.

In a series of experiments Gershwin and Corbeil showed that dual infection with BRSV and *Histophilus somni* induced IgE antibodies to *H. somni* (Gershwin et al., 2005). The specificity of these antibodies was determined by western blot (Corbeil et al., 2006). The severity of disease, as measured by clinical signs, lung pathology, and isolation of *H. somni* at necropsy day 28 after experimental infection, correlated with the presence of *H. somni* specific IgE in serum. Current studies are directed at examining the role of this IgE in disease pathogenesis.

7. IgE responses to protozoa

In human females infected with *Trichomonas vaginalis* an IgE response in the mucosal secretions has been demonstrated. In that location a protective role of IgE as a “gatekeeper” antibody causing increased capillary permeability and increased IgG concentrations in the interstitial fluid has been hypothesized (Su, 1982). Studies on bovine trichomoniasis have similarly identified the presence of IgE antibodies in uterine and vaginal secretions of infected heifers (Corbeil et al., 2005). In a study by Shin et al. (2004) IgE antibodies reactive with proteins of *Neospora caninum* were identified by western blot in sera from infected cattle.

8. Clinical allergy in cattle

There is surprisingly little documentation of naturally occurring allergic disease in cattle. In one of the few cases described allergic rhinitis was identified in a herd of Hereford cattle. The disease was characterized by rhinitis, sneezing and nasal pruritus. Histological examination of the nasal tissue showed a predominance of eosinophils. Both intradermal injection of allergens and IgE allergen specific ELISA demonstrated an IgE-mediated response to environmental allergens (Olchoway et al., 1995).

A role for IgE in eosinophilic myositis was documented in cattle by Grandstrom. He found IgE specific for *Sarcocystis cruzi* in serum of affected cattle and by immunofluorescent localization in the muscle lesions (Granstrom et al., 1989, 1990).

An IgE response to milk proteins, such as lactalbumin and casein, has been described in high producing dairy cattle. A clinical outcome of anaphylaxis was attributed to milk proteins entering the circulation due to high pressure in the udder when the affected cow was not regularly milked (Tizard, 2009).

9. Vaccination associated IgE responses

The anaphylactic response to vaccine components has been recognized with several different preparations. In the 1960s cases of allergic reactivity to vaccination with foot-and-mouth disease vaccine were documented (Makarova and Intizarov, 1966; Black, 1977). Proteins from baby hamster kidney cells and other constituents used in the vaccine, rather than the virus itself, were identified as antigens that elicited IgE in reactive cattle.

Bovine respiratory syncytial virus vaccine has been associated with development of IgE antibodies specific for viral proteins. In experimental studies IgE antibodies specific for BRSV were associated with BRSV enhanced disease in a studies by our group (Kalina et al., 2004) and by Antonis et al. (2003). However, field cases of vaccine reactions with clinical signs of anaphylaxis have been reported and the presence of IgE has been verified by using BRSV specific IgE ELISA (unpublished data, Gershwin Laboratory).

Vaccination hypersensitivity reactions associated with *H. somni* (formerly *Haemophilus somnus*) bacterins were seen in field studies, prompting Ruby et al. (2000) to

examine the induction of *H. somni* specific IgE to these vaccines. An IgE response was demonstrated in cattle vaccinated with all four monovalent *H. somni* bacterins tested. Later studies by our group showed that vaccination with an *H. somni* bacterin with and without concurrent BRSV vaccination enhanced a protective IgG2 response to *H. somni* which inversely correlated with clinical severity of disease in dually infected calves. Whereas killed BRSV vaccine induced IgE antibodies which directly correlated with disease severity in challenged calves (Berghaus et al., 2006). The differences in composition of bacterins (amount of antigen and type of adjuvant) have a great influence on the type of immune response evoked. In addition, multiple studies in our laboratory have demonstrated the role of individual variability (genetic variation) in IgE responsiveness.

An experimental vaccine developed against a purified capsular polysaccharide *Mannheimia hemolytica* (formerly *Pasteurella hemolytica*) induced anaphylactic reactions and IgE responses were detected in serum (Conlon and Shewen, 1993). In our earlier study (mentioned above) in which IgE antibodies to *P. hemolytica* were found in sera of normal dairy cows, we found that calves immunized parenterally with a *P. hemolytica* bacterin failed to make an IgE response (Gershwin and Friebertshauser, 1987).

10. Summary

The availability of reagents to detect bovine IgE has facilitated the documentation of its presence: in response to antigen aerosol, during helminth, bacterial, viral, and protozoan infections, and in response to some vaccines. Undoubtedly as more investigators become interested in bovine IgE responses the role of this antibody in disease will be more fully elucidated.

Conflict of interest statement

None.

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