

EDITORIAL

Glucocorticoids enhance IgE synthesis. Are we heading towards new paradigms?

Atopy, which is defined as an inherited predisposition to produce abnormal amounts of immunoglobulin (Ig) E in response to contact with allergens, is considered to be one of the strongest risk factors associated with allergic diseases. Elevated levels of circulating IgE almost invariably accompany asthma, allergic rhinitis and atopic dermatitis, with increased levels of IgE commonly being used as a guide for diagnosis, environmental modification and immunotherapy. Previous epidemiological studies have demonstrated an association between circulating levels of total IgE and airway hyperresponsiveness (AHR), prevalence of asthma and asthma severity [1,2]. Furthermore, both total and allergen-specific IgE have consistently been found to be present in airway secretions from human patients with allergic rhinitis and asthma [3,4]. Laboratory studies have demonstrated that receptor cross-linking of membrane-bound IgE on mast cells and basophils leads to rapid release of both preformed and newly synthesized mediators, such as histamine, leukotrienes, prostaglandins, neutral proteases such as tryptase and pro-inflammatory cytokines. Each of these substances has been implicated in different aspects of the acute phase reaction as well as in recruiting inflammatory cells that drive the chronic phase of allergic disease [5]. These observations have led to the belief that IgE plays a central role in the initiation and perpetuation of the allergic disease [6,7].

Glucocorticoids are regarded as the most effective drugs for treatment of allergic disorders, including asthma, atopic dermatitis, allergic rhinitis. The most widespread use of glucocorticoids is in asthma, where inhaled and oral preparations have revolutionized asthma treatment and according to management guidelines have become the mainstay of therapy for patients with all grades of asthma severity. Generally, quite marked and rapid clinical improvements and changes in lung functions can be seen with relatively low doses of corticosteroids given daily. Higher doses reduce airway hyperresponsiveness as well as the numbers of activated eosinophils, mast cells and T-lymphocytes. Although glucocorticoids generally suppress innate immunity, their action on the cellular and humoral response is more complex. The cellular immune response is strongly suppressed by glucocorticoids, whereas the humoral immune response is either poorly inhibited or even

enhanced [8]. The effects of glucocorticoids on IgE synthesis and IgE-mast cell-mediated responses have been controversial. Skin test reactivity to allergens is not altered by treatment with either short periods [9] or even prolonged periods of systemic steroid administration [10], thereby suggesting that they do not affect allergen-specific IgE or IgE-mast cell-mediated responses *in vivo*.

In this issue, Cho *et al.* [11] have demonstrated that hydrocortisone enhances total and allergen-specific IgE production by peripheral blood mononuclear cells from atopic subjects *in vitro*. Moreover, the induction of house dust mite-specific IgE synthesis in subjects with high serum allergen-specific IgE levels was even greater than that of IL-4. Although, previous studies have reported that glucocorticoids enhance total IgE production, this is the first report to show that hydrocortisone enhances dust mite-specific IgE production from circulating B cells in atopic asthma. The immediate *in vivo* interpretation of these findings would be that glucocorticoids promote allergy, which in theory would mean that the most efficacious treatment for allergic diseases is detrimental regarding disease progress. However, is this a true effect? If so, what is the underlying mechanism by which glucocorticoids enhance IgE production? And what do these findings really mean with regard to the current paradigm for the role of IgE and glucocorticoids in asthma?

Glucocorticoids enhance IgE synthesis *in vitro*, *ex vivo* and *in vivo*

Glucocorticoids (hydrocortisone, prednisolone, dexamethasone) have been shown to enhance IL-4-induced IgE synthesis by peripheral blood mononuclear cells and purified B cells from atopic as well as nonatopic healthy subjects *in vitro* as well as *ex vivo* by several workers (Table 1). This effect is specific for glucocorticoids and is not observed with other steroid molecules [12]. The IgE potentiating effect varies between two and 100-fold and occurs at low concentrations of hydrocortisone, levels that are comparable to those found in plasma during systemic or inhaled administration.

Glucocorticoids have also been shown to enhance IgE synthesis *in vivo*. Earlier work by Settipane *et al.* [13] and Posey *et al.* [14] have demonstrated that oral prednisolone increases both total and allergen-specific circulating IgE levels, suggesting that the rise in IgE is polyclonal in nature. The levels of IgE return to normal after discontinuation of

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Table 1. Effect of glucocorticoids on IgE

Cells analysed	Glucocorticoids studied	Dose	Effects	Reference
<i>Non-atopics</i>				
PBMC's	Hydrocortisone	10^{-5} – 10^{-9} M	↑ Total IgE (in the presence of IL-4)	[12]
B-cells (blood, tonsils & spleen)	Dexamethasone			
PBMC's	Prednisolone			
Peripheral blood B-cells	Hydrocortisone	10^{-4} – 10^{-7} M	↑ Total IgE (in the presence of IL-4)	[18,19]
PBMC's	Hydrocortisone	10^{-5} – 10^{-7} M	↑ Total IgE	[20,66]
		10^{-3}	↓ Total IgE	
PBMC's	Prednisolone	10^{-7}	↑ Total IgE (not mediated by IL-4/IL-6)	[67]
PBMC's	Hydrocortisone	10^{-5} – 10^{-7} M	↑ Total IgE	[21]
	Dexamethasone			
	Prednisolone			
<i>Atopics</i>				
Peripheral blood B-cells	Hydrocortisone	10^{-7} – 10^{-9} M	↑ IgE	[68]
		10^{-5}	↓ IgE	
	Beclomethasone		↑ Total IgE	[69]

↑, increased; ↓, decreased.

the drug. More recently, it has been reported that both short-term (prednisolone 40 mg/day for 7 days) and long-term (prednisolone 20 mg/day for 2 years) glucocorticoid administration increases total as well as allergen-specific circulating levels of IgE *in vivo* [10,15]. Glucocorticoids do not suppress skin test reactivity to allergens, and in fact, 50% of the patients receiving long-term oral steroids have been reported to develop new allergic sensitivities [10]. In a mouse model, Bargatze *et al.* [16] have demonstrated a correlation in the normal diurnal variation of endogenous cortisone production and the cyclical pattern of IgE synthesis after antigen sensitization at various times of the day, and have suggested that judicious caution should be followed in avoiding exposure to potential sensitizing allergens during the course of steroid therapy. Glucocorticoids suppress IgE *in vivo* only when given in very high doses [17].

These studies therefore suggest that the increase in IgE synthesis produced by glucocorticoids occurs both *in vitro* and *in vivo*.

How do glucocorticoids increase IgE synthesis?

IgE synthesis requires at least two distinct signals. The first signal is provided by the cytokines IL-4 or IL-13, which stimulate transcription of the C ϵ gene locus containing the exons encoding the constant region domains of the IgE ϵ -heavy chain. The second signal activates the genetic

arrangement (deletional switch recombination) that brings into proximity all the elements of a functional ϵ -heavy chain. This second signal can be delivered by T cells, Epstein–Barr virus or engagement of CD40 [18]. Hydrocortisone has been shown to induce S μ to S ϵ deletional switch recombination in IL-4-treated B cells, thereby causing sequential switching from IgM to IgE via IgG4 [18]. Initial studies suggested that glucocorticoids enhance IgE synthesis from B cells only in the presence of T cells or monocytes [19], probably by enhancing Th2 cytokines synthesis or by inhibiting the production of IFN γ . However, addition of antibodies directed against IL-4 or IL-5 have not been shown to suppress hydrocortisone-induced IgE synthesis [12]. Several studies have shown that glucocorticoids enhance IL-4 induced IgE synthesis when added to pure B cell cultures in the absence of T cells or monocytes [18,20,21].

B lymphocytes that are already switched to IgE production are no longer dependent on IL-4 for IgE synthesis [22]; further stimulation with glucocorticoids then enhance IgE synthesis even in the absence of IL-4 [11]. *In vitro* studies have shown that HC increases the production of IgE even when added up to day 6 of cultures, in contrast to IL-4, which increases IgE only when added during the first 4 days. It has been suggested that glucocorticoids facilitate the maturation of IgE B cells to plasma cells resulting in greater IgE secretion [23–25]. This viewpoint is also supported by the observation that glucocorticoids induce differentiation

of B cell chronic lymphocytic leukaemia (cells that are arrested at the intermediate stage of their differentiation) into IgE producing plasma cells and enhance IgE synthesis in the presence of IL-4 [26].

In summary, corticosteroids therefore enhance IgE synthesis by inducing $S\mu$ to $S\epsilon$ deletional switch recombination in IL-4-treated B cells and by facilitating the maturation of IgE B cells to plasma cells.

Do these studies suggest that glucocorticoids worsen the underlying disease state?

Clinical experience dictates that glucocorticoids are the most effective drugs used in the management of allergic diseases. Glucocorticoid-induced enhancement of IgE synthesis occurs despite producing significant improvement in symptoms and pulmonary function changes. In asthma, glucocorticoid inhalation results in a dose- and time-dependent reversal of bronchial hyperresponsiveness and other clinical outcome measures towards normal [27], while introduction of steroid therapy earlier in disease progression has been shown to produce better long-term outcomes for lung function [28]. Biopsy studies have clearly demonstrated that corticosteroids are the most effective drugs in reducing the underlying inflammatory changes seen in asthma and rhinitis.

These clinical and laboratory observations do not support the view that corticosteroids worsen the underlying allergic process. However, the clinical relevance of these observations needs to be examined seriously in future studies. The other possibility would be that IgE does not play a major contributing role in the pathogenesis of allergic diseases. Do epidemiological and laboratory studies support this possibility?

Do epidemiological studies suggest an important role for IgE in asthma pathogenesis?

Early epidemiological studies reported a strong correlation between serum total IgE levels and the prevalence of asthma [1,2]. However, determination of the presence/absence of asthma in these studies was crude and based entirely on information from questionnaires. Recent studies from Australia [29], China [30] and Africa [31] have shown little or no association between the prevalence of atopy and diagnosed asthma. A recent large randomized sample of Swiss adult population (SAPALDIA study) has demonstrated that total IgE is a poor diagnostic indicator of current respiratory allergic diseases [32]. Studies in Africa have found a generally lower prevalence of self-reported asthma symptoms, exercise-induced bronchoconstriction and allergic rhino conjunctivitis, although they all have higher IgE levels [31,33,34]. In fact, in the African population serum

levels of IgE have been reported to be higher in nonasthmatics than asthmatics [35]. Although this has been argued to be due to high parasite burdens and that parasite specific IgE block allergic response, several studies do not support the parasite-protective hypothesis [36,37], and there is also evidence to suggest that parasitic infection actually increases the risk [35].

Standardized comparisons across populations or time periods show only a weak and inconsistent association between the prevalence of atopy and asthma [38]. Recent analysis of several published studies have shown that the population attributable risk of atopy (defined as raised total serum IgE level) for asthma varies between less than 0% (an inverse association) to 80% with a weighted mean of 33% [38]. As the definition of atopy is strengthened, the association of asthma also strengthens, but the population attributable risk decreases to 3% because of the reduction in the proportion of population that is positive. The available epidemiological studies suggest that the population-based proportion of asthma cases that are attributable to atopy is usually less than one half, and it has been suggested that the proportion of asthma cases attributable to atopy may have been over estimated and that atopy may not explain all the pathogenesis of asthma as has been currently believed [38].

Laboratory evidence suggesting that IgE does not play an important role in asthma pathogenesis

Despite the putative functions of IgE in asthma, it has been difficult to demonstrate a precise role for this immunoglobulin isotype in the pathogenesis of asthma using murine models of the disease. Inflammation of the bronchial mucosa and the induction of bronchial hyperresponsiveness have been shown to be elicited to the same extent in wild-type and IgE-/- knockout mice subjected to repeated inhalation of allergen extracts [39]. Hamelman *et al.* [40] have demonstrated that intraperitoneal sensitization plus repeated airway challenge of B cell-deficient mice with allergen results in normal eosinophilic airway inflammation and development of airway hyperresponsiveness, both *in vivo* and *in vitro*. Similarly, use of anti-IgE antibody in the wild-type mice does not prevent airway inflammation and airway hyperresponsiveness [41]. These data indicate that neither B cells nor allergen-specific antibodies (IgE or other isotypes) are required for the recruitment and activation of eosinophils in the airways that result in the development of airway hyperresponsiveness in sensitized and challenged animals. Tournoy *et al.* [42] have recently demonstrated that induction of airway hyperresponsiveness and late phase airway obstruction following house dust mite allergen challenge in a mouse model of asthma is not related to the quantity of circulating allergen-specific IgE, and suggest that IgE is not essential for the development of allergic airway hyperresponsiveness.

Although the role of IgE is best characterized in the pathogenesis of anaphylaxis, active anaphylaxis with mast cell activation and mediator release has been demonstrated in mouse models by both allergen sensitized IgE^{-/-} and FcεRI^{-/-} deficient mice after intravenous challenge with allergen [43,44]. Similarly, allergic rhinitis and atopic dermatitis also arise independently of the presence of IgE in mice.

Based on these data the exact role of IgE in allergic diseases, in particular asthma, have yet to be fully understood.

Anti-IgE studies in humans

The concept that allergen-specific IgE initiates allergic airway symptoms has driven the development of therapeutics such as eliminating IgE with a blocking monoclonal antibody approach. Although initial studies demonstrated that anti-IgE monoclonal antibody suppressed the early and late phase responses to inhaled allergen in allergic asthmatic subjects as measured by mean maximal fall in FEV₁ and the dose of allergen required to induce a fall in FEV₁ by 15% [45,46], aerosol administration of anti-IgE antibody by the same group demonstrated no more efficacy than placebo in attenuating the early phase responses to allergens [47]. Casale *et al.* [48] reported that humanized anti-IgE monoclonal antibody, although greatly reduced circulating levels of free IgE, did not produce any beneficial effect on symptom scores in ragweed sensitive allergic rhinitis. Nevertheless, recombinant humanized monoclonal anti-IgE has been observed to have a corticosteroid sparing effect in moderate-severe asthmatics [49]. More recently, Milgrom *et al.* [50] have reported that a recombinant humanized monoclonal anti-IgE antibody greatly reduces circulating levels of IgE in moderate asthma subjects and improves asthma symptoms as well as allowing a reduction in oral and inhaled corticosteroid use. However, the differences in symptom scores between the active and placebo group were marginal, and there were no changes observed in objective parameters such as standard lung function measurements (FEV₁ and PEF) [51].

Overall, recent studies suggest that the effect of anti-IgE antibody on bronchial hyperresponsiveness induced by methacholine is only modest. Clinical measures of chronic asthma are not significantly different between anti-IgE antibody-treated individuals and controls and there are no differences in peak flows, medication scores or symptom scores [52].

Other therapies effective in asthma and allergy also enhance IgE synthesis

Coqueret *et al.* [53,54] and others [55] have previously reported that β₂-adrenoreceptor agonists (salbutamol and

fenoterol) potentiate the IL-4 induced IgE production from normal human peripheral blood mononuclear cells *in vitro* at concentrations which would normally be found in plasma. Similarly, other cAMP elevating agents such as vasoactive intestinal peptide (VIP) [56], cholera toxin [57], prostaglandin E₂ [58] and phosphodiesterase enzyme inhibitors [59] have all been shown enhance IgE synthesis *in vitro*. Allergen immunotherapy, which has recently been found to be greatly effective in relieving symptoms of allergic rhinitis, has also been shown to be associated with increased levels of both total and allergen-specific IgE [60–63]. It has been recently suggested that the predictive value of specific IgE present in serum is questionable with regard to organ-based manifestations of allergy in that a certain level of specific-IgE does not provide any information about the level of sensitization existing in a target organ such as airways [64].

While substantial evidence exists to support the view that IgE plays an important and sometimes necessary role in the development of airway hyperresponsiveness and airway pathology, it is likely that a number of parallel mechanisms participate in asthma pathogenesis. Although IgE is uniquely important in the acute allergic response, it represents only one component of the ongoing chronic allergic inflammatory response. It is likely that IgE may be required for pathogenesis in some circumstances while functioning as an accessory or regulatory factor in other. Sunyer *et al.* [65] have suggested that co-inherited genetic factors could increase susceptibility both to asthma and to the production of raised serum IgE levels and that total serum IgE levels could in part be a marker of asthma itself. Future studies will now need to address the issue whether the association between raised levels of circulating IgE in allergic disorders represents an underlying causal mechanism of allergic diseases or a parallel but related phenomena and whether it is influenced by pharmacotherapy.

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