Clin. exp. Immunol. (1990) **79**, 380–384

Depressed lymphocyte transformation and the role of prostaglandins in atopic dermatitis

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(Accepted for publication 18 October 1989)

SUMMARY

We have shown that peripheral blood mononuclear cells (PBMC) from patients with atopic dermatitis have a reduced *in vitro* proliferative responsiveness to concanavalin A when compared with non-atopic controls. Addition of the cyclo-oxygenase inhibitor indomethacin caused a significant enhancement of the mitogen response in the patients, indicating a suppressive effect of cyclooxygenase products. We have further demonstrated increased levels of prostaglandin E_2 in the supernatants of the PBMC cultures and increased levels of IgE immune complexes in the sera of the atopic dermatitis patients and therefore hypothesize that IgE immune complexes may cause increased monocyte production of prostaglandins which in turn appears to be responsible for a reduced lymphocyte proliferation.

Keywords atopic eczema lymphocytes IgE immune complexes prostaglandins

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder of early infancy, childhood, adolescence and adult age, characterized by severe pruritus, lichenification and eczematous lesions. AD is often associated with a personal history of atopy, increased susceptibility to cutaneous viral or bacterial infections and various immunological abnormalities, including elevated serum IgE level, circulating IgE immune complexes, decreased numbers of T suppressor cells and depressed cell-mediated immunity to common skin test antigens (reviewed by Leung & Geha, 1986). A depressed lymphocyte response to T cell mitogen *in vitro* has been described (Lobitz, Honeyman & Winkler, 1972; McGeady & Buckley, 1975; Elliot & Hanifin, 1979) and suggested to reflect the cutaneous anergy observed *in vivo*. These findings are not solely a function of the atopic status of the patients in this study, as individuals with asthma or hay fever but without AD give normal mitogenic responses (Hall, Hudspith & Brostoff, 1983).

Evidence has also been obtained for an abnormal monocyte function in AD. Thus monocyte chemotaxis has been shown to be depressed (Rogge & Hanifin, 1976), a decreased natural killer cell activity has been suggested to be due to a suppressive effect of monocytes (Jensen *et al.*, 1984) and more recently an impaired monocyte interleukin-1 (IL-1) production has been demonstrated (Mizogguchi *et al.*, 1985; Räsänen *et al.*, 1987). In the past, various studies have implicated the regulation of the immune response by prostaglandins (reviewed by Goodwin & Webb, 1980). It was shown that prostaglandins of the E series inhibit mitogen-induced lymphocyte proliferation. Cells of the monocyte/macrophage lineage are a major source of prostaglandin (PG) E. PGE_2 can inhibit IL-1 production of mononuclear phagocytes (Hudspith *et al.*, 1984; Kunkel, Chensue & Phan, 1986).

Here we demonstrate that the depressed lymphocyte mitogen response observed in AD can be partially reversed by the inhibition of cyclo-oxygenase and that it appears to relate to an increased monocyte production of PGE_2.

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MATERIALS AND METHODS

Patients

We studied 31 patients (19 women and 12 men; mean age 28·9 years, range 10–58), who fulfilled the criteria of Hanifin & Lobitz (1977) for the diagnosis of AD. None of the patients received systemic corticosteroids at the time of the study, nor during the 4 weeks before blood collection. The control group consisted of 21 non-atopic volunteers (13 men and eight women; mean age 32·3, range 21–55) with no history of atopic diseases.

Lymphocyte transformation of human peripheral blood mononuclear cells (PBMC)

Heparinized venous blood was diluted 1:1 with balanced salt solution (BSS) and layered onto lymphoprep gradient (Nycomed, Oslo, Norway) and centrifuged at 400 *g* for 30 min at room temperature. The total mononuclear cells were recovered

from the interphase, washed twice in BSS, counted after acridine-orange/ethidium-bromide (Sigma, Poole, UK) staining and resuspended in RPMI 1640. Total mononuclear cells were plated into flat-bottomed microtitre plates to give a final concentration of 2×10^5 cells/well in 200 μl RPMI 1640/10% fetal calf serum (FCS; Northumbria Biologicals, UK). A suboptimal dose (5 μg/ml) of concanavalin A (Con A; ICN Pharmaceuticals, Cleveland, OH) and optimal indomethacin (Sigma) (1 μg/ml) were added at the initiation of the culture. The cells were incubated at 37°C, 5% CO_2 in a humidified cell incubator for 3 days, pulsed with ^{3}H-thymidine (Amersham International, Amersham, UK), at 0·4 μCi/well, for the final 16 h of the culture, harvested onto glass fibre disks using a Titertek harvester. The disks were then placed in scintillation fluid (Ecoscint A; National Diagnostics, UK) and counted using a Packard β-counter. All determinations were performed in triplicate and results expressed as mean ± s.e.m. (< 10%).

Assay for PGE_2

Supernatants obtained from the lymphocyte transformation of human mononuclear cells after 36 h of culture were diluted 1:20 in assay buffer and assayed for PGE_2 using the Du Pont (Dreieich, FRG) PGE_2 ^{125}I-radioimmuno assay (sensitivity < 1 pg PGE_2/ml). The culture medium (RPMI 1640/10% FCS) was tested for interference with the assay system and found to contain a PGE_2 activity of less than 4% of the activity detected in supernatants of background lymphocyte cultures. Consequently the PGE_2 standard solutions were prepared in a 1:20 solution of RPMI 1640/10% FCS:assay buffer.

Total serum IgE and IgE immune complexes

Serum obtained from normal clotted peripheral venous blood of patient and control subjects was tested for total serum IgE using IgE ELISA as previously described (Scadding & Brostoff, 1985). IgE containing immune complexes were detected via precipitation with polyethylene gycol (modified after Creighton, Lambert & Miescher, 1973). Briefly, serum was added in 150-μl aliquots to 12% polyethylene glycol 6000 (PEG; BDH chemicals, Poole, UK) in veronal-buffered saline (VBS), 0·06 M EDTA, to give a final concentration of 2% PGE. The samples were incubated for 16 h at 4°C and spun at 1000 ***g*** for 20 min at 4°C. The supernatants were removed and the precipitates washed in 2% PEG by centrifuging under the same conditions. The resulting precipitates were resuspended in 150 μl VBS, incubated for 1 h at 37°C and then stored at −20°C for assay. Samples of each patient were tested in triplicate for IgE content using IgE ELISA.

Statistical analysis

Significance testing of the results obtained in the lymphocyte transformation test was performed using the paired and unpaired Student's *t*-test. Estimates of the significance of the PGE_2 results were obtained using the Wilcoxon signed rank test for paired data and the Mann–Whitney *U*-test for unpaired data.

RESULTS

Lymphocyte Transformation

The Con A-induced proliferation of PBMC obtained from the AD patients (4667 ± 307 s.e.m. ct/min) was found to be significantly lower than the response obtained from non-atopic control subjects 7285 ± 356 ct/min; $P < 0.001$). No significant difference was detected between the background proliferation of the PBMC of both groups (Fig. 1).

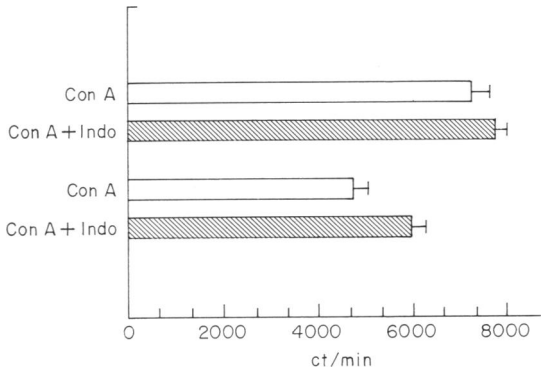

Fig. 1. The effect of indomethacin (Indo) on ^{3}H-thymidine incorporation in 31 patients with atopic dermatitis (bottom) and 21 control subjects (top). Ct/min s.e.m. obtained after 3-day culture of peripheral blood mononuclear cells stimulated with 5 μg/ml concanavalin A (Con A) in the presence or absence of 1 μg/ml Indo.

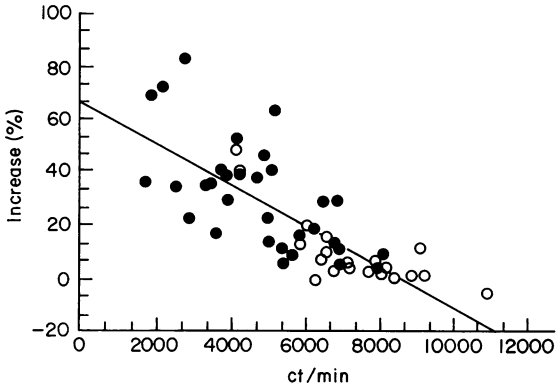

Fig. 2. The effect of indomethacin on ^{3}H-thymidine incorporation in 31 patients with atopic dermatitis (●) and 21 control subjects (○) expressed as % enhancement of and plotted against the ct/min obtained with mitogen stimulation alone. Mean enhancement in patients (32·48 ± 3·96% s.e.m.) was significantly higher than in controls (mean 8·77 ± 2·85%; $P < 0.001$). The degree of enhancement by indomethacin was significantly ($P = 0.001$) correlated ($r = -0.78$) with the response obtained with mitogen alone.

Restorative effect of indomethacin on mitogenic response

We found that indomethacin significantly enhanced the Con A response of AD lymphocytes by more than 30% ($P < 0.001$), whereas in the control group it only caused an augmentation of less than 10% (Fig. 1). Indomethacin did not appear to affect the background proliferation of non-stimulated PBMC in both groups. The specific inhibition of cyclo-oxygenase thus appeared to have a restorative effect on the depressed lymphocyte proliferation observed in AD. Pooling the data of the investigated groups we found a significant correlation between the Con A-induced thymidine incorporation and the percent increase obtained after indomethacin treatment ($r = -0.78$) (Fig. 2). The

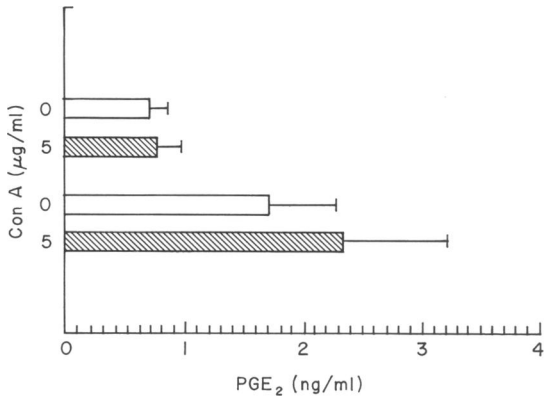

Fig. 3. Prostaglandin (PG) E_2 levels determined in the supernatants of peripheral blood mononuclear cells cultures of nine controls (top) and nine patients with atopic dermatitis (bottom) after 36 h of incubation with top (▨) or without bottom (□) μg/ml concanavalin A (Con A) stimulation. The PGE_2 production in atopic dermatitis after Con A stimulation was found to be significantly ($P<0.05$) higher than in the control group (2·33 pg/ml ± 0·9 s.e.m. and 0·79 pg/ml ± 0·19 s.e.m., respectively).

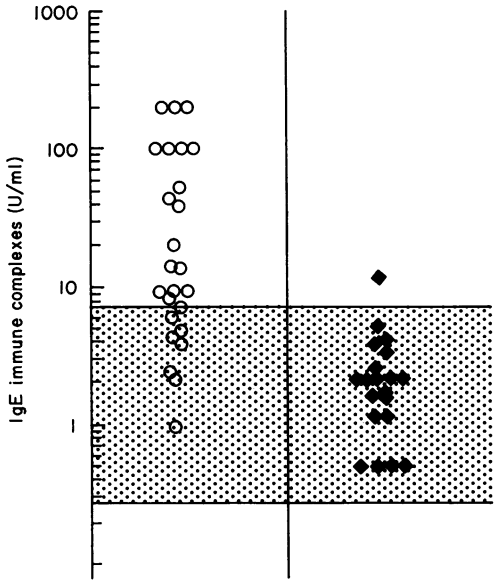

Fig. 4. IgE immune complexes in sera of 25 atopic dermatitis patients (●) after precipitation with 2% polyethylene glycol; 68% of the sera showed abnormal high levels of IgE immune complexes. The cut-off point for normal had been determined as 7 U/ml (mean ± 2 s.d.) using 20 non-atopic controls (○).

restorative effect of indomethacin therefore seems to depend on the degree of depression of the proliferative response to Con A and clearly suggests the involvement of cyclo-oxygenase products in the aetiology of the latter phenomenon.

PGE_2 levels

PGE_2 levels measured in supernatants of the AD PBMC cultures after mitogen stimulation were found to be significantly higher than the levels obtained in the control group ($P<0.05$) (Fig. 3). The background PGE_2 production, i.e. the PGE_2 levels measured in supernatants after incubation without mitogen, also appeared to be higher in AD than in controls; however, this observation was not statistically significant. No significant correlation could be obtained between the PGE_2 levels and the mitogenic response of the PBMC or the restorative effect of indomethacin.

IgE immune complexes in sera of AD patients

High levels of IgE immune complexes were detected in 68% of the AD sera (range 8·3– > 100 U/ml; $n=25$) after precipitation with PEG (Fig. 4). The cut-off point for normal has been determined as 7 U/ml (i.e. mean ± s.d.), using a non-atopic control group (mean 2·53 U/ml ± 2·23 s.d.; $n=20$). IgE immune complexes were found to be significantly correlated with the serum IgE levels ($r=0.746$; $P=0.001$), which were found to be increased in 89% of the AD sera (mean 11925 U/ml ± 2769 s.e.m.; $n=28$). It was found that 76% of the patients with increased levels of IgE immune complexes also showed a clearly reduced lymphocyte proliferation as shown by the mitogen assay. However, no significant correlation could be obtained between the IgE immune complexes and the mitogen response, the restorative effects of indomethacin or the PGE_2 levels in the supernatants of the PMBC cultures.

DISCUSSION

The depressed lymphocyte responsiveness, observed in this study is a well-documented phenomenon in patients with AD (Lobitz *et al.*, 1972; McGeady & Buckley, 1975; Elliot & Hanifin, 1979), which may represent an intrinsic lymphocyte defect but equally may be due to some extracellular mechanism associated with the disease.

We have now shown that inhibition of the cyclo-oxygenase pathway enhances the mitogen response to a greater extent in AD than in non-atopic controls. This enhancement is strongly correlated with the degree of depression of the lymphocyte response and restored the lymphocyte response partially back to normal. A sub-optimal dose of the mitogen was used in these experiments because we were looking for enhancement of a response but this effect to show this effect which was not seen in the control group, a sub-optimal dose was used as a maximal response cannot be enhanced. Our results suggest that cyclo-oxygenase products are involved in the suppression. We have measured PGE_2 levels in the supernatants of the lymphocyte transformation and detected increased levels of PGE_2 in the AD group. Although there is no significant correlation between PGE_2 concentrations and the depression of the mitogen responsiveness, we do suggest that the depressed lymphocyte response in AD may be secondary to a primary monocyte overproduction of PGs.

It has been shown that PGs, especially those of the E series can inhibit lymphocyte proliferation *in vitro* (Goodwin, Bankhurst & Messner, 1977) and that the monocytes appear to be the major cell fraction of the PBMC producing these PGs (Kurland & Bockman, 1978). Our previous studies (Hudspith *et al.*, 1984) have shown that exogenous PGE_2 in the micromolar range can inhibit the IL-1 production of human monocytes. The concentrations of PGE_2 measured in the present study were 10–100-fold lower than the concentrations of exogenous PGE_2 added to obtain significant inhibition of IL-1 production. This difference may be accounted for by the fact that we measured the PGE_2 level in the supernatants of the full PBMC, which may underestimate the local concentrations produced by and acting

on the monocytes. The PGE_2 and IL-1 production of the monocyte fraction of the PBMC in AD in the presence and absence of indomethacin is currently under investigation.

Consistent with our previous study in humans, an inverse relation between IL-1 levels and PGE_2 production and a suppressive effect of exogenous PGE_2 ($>10^{-8}$ M) on IL-1 production has also been reported in murine mononuclear phagocytes (Kunkel *et al.*, 1986). PGE_2 thus appears to act as a negative feedback modulator on the production of IL-1, a monokine required for the activation of T lymphocytes. In this context it has recently been demonstrated (Mizoguchi *et al.*, 1985; Räsänen *et al.*, 1987) that monocytes of AD patients produce decreased concentrations of IL-1. However, the effect of cyclo-oxygenase inhibitors in this phenomenon has not been investigated. Our observation that inhibition of PG synthesis partially but not completely reversed the mitogen responsiveness may indicate the existence of a second PG-independent mechanism. In addition to the inhibitory effect on the IL-1 production, PGE_2 has also been reported (Rappaport & Dodge, 1982) to decrease the production of IL-2, a lymphokine required for T cell proliferation. Furthermore, PGs of the E series have been shown (Jensen *et al.*, 1984; Hall, Rycroft & Brostoff, 1985) to reduce natural killer cell activity in patients with AD, as well as being a potent inhibitor of macrophage Ia expression (Snyder, Beller & Unane, 1982; Kunkel *et al.*, 1984), a glycoprotein essential for the cognate cellular interactions during the process of antigen presentation. Increased levels of PGE_2 in AD thus may not only be a cause of the depressed mitogenic lymphocyte response, but may also provide a plausible explanation for the cutaneous anergy observed in AD.

Elevated cyclo-oxygenase products in AD may be due to an intrinsic defect of the monocytes or may be initiated by a factor associated with the disease.We have shown increased levels of IgE IC in 68% of the AD sera which may be a function of the increased serum IgE levels, since a significant correlation could be shown between the level of total IgE and IgE immune complexes. Although we could not demonstrate a significant correlation between the IgE immune complexes and the PGE_2 levels or the depression of the lymphocyte responsiveness, the work of various other investigators suggest that these abnormal high concentrations of IgE immune complexes may be related to the increased level of PGE_2 in AD. Incubation of human alveolar macrophages with IgE and subsequently with anti-IgE induced increased lysosomal enzyme release (Joseph *et al.*, 1980). Similarly, IgE immune complexes were shown (Rouzer *et al.*, 1982) to induce increased arachidonic acid metabolism and PGE_2 production in rodent macrophages. It has also been demonstrated (Passwell *et al.*, 1984) that the addition of isolated human IgE, obtained from a patient with hyper-IgE syndrome, to a monolayer of normal human monocytes can lead to increased PGE_2 production. This phenomenon was markedly enhanced when F(ab′) goat anti-human IgE was added, whereas no enhancement was observed when irrelevant $F(ab')_2$ fragments of goat IgG were used, indicating that IgE in a complexed form may lead to an activation of the monocytes possibly via the cross-linking of its IgE receptors.

Low-affinity Fc receptors for IgE (FcεR II) have been demonstrated on macrophages as well as on monocytes (Melewicz & Spiegelberg, 1980; Boltz-Nitulescu, Plummer & Spiegelberg, 1982) and it has been shown that the number of FcεR bearing peripheral blood monocytes is increased in patients with allergic disorders and high serum IgE (Melewicz *et al.*, 1981). In this context Bruynzeel-Koomen *et al.* (1986, 1988) as well as Bieber, Ring & Rieber (1987) have shown both IgE and FcεR II on skin Langerhans cells, and Leung *et al.* (1987) have also reported that a substantial proportion of macrophages infiltrating the skin lesions of AD bear IgE on their cell surface. Thus it may be that deposition of IgE immune complexes in the skin of AD patients, as has been demonstrated for other isotypes and complement (Ring *et al.*, 1979), are potentially capable of inducing the release of macrophage mediators causing cutaneous anergy and inflammatory skin reactions observed in AD. Although we found no correlation between serum IgE immune complexes levels and the lymphocyte tests it is possible that binding of the immune complexes has taken place *in vivo* and so the serum levels would not be relevant as it is the cell-bound immune complex that is important.

We feel that there may be a number of inter-related immunological abnormalities in patients with AD and that an important factor among those abnormalities may be inappropriate activation of monocytes by immune complexes *in vivo*.

ACKNOWLEDGMENT

This study is part of the inaugural dissertation of T.J. at the Ludwig-Maximilian-University of Munich, FRG.

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