

Impaired Monocyte Cyclic AMP Responses and Monocyte Cytotoxicity in Atopic Dermatitis

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Purified monocytes from 21 patients with mild and severe atopic dermatitis (AD) were compared with 22 healthy controls with respect to antibody-dependent cell-mediated cytotoxicity (ADCC) and cyclic adenosine 3',5'-monophosphate (cAMP) responses to stimulatory agents. ADCC was depressed in both severe and mild atopic dermatitis. The patients showed decreased cAMP responses to isoproterenol and histamine, the decrement being more distinct in severe atopic dermatitis. Formation of cAMP was diminished with PGE₁ only in patients with severe AD. ADCC is inhibited by the agents that increase cAMP. In the severe dermatitis group reduced inhibition induced by isoproterenol, histamine, but not PGE₁, was obtained. It is suggested that a general suppression of membrane activation may explain the reduced cAMP responses to various stimulatory agents and the impaired monocyte cytotoxicity.

Key words: atopic dermatitis; antibody-dependent cell-mediated cytotoxicity; cyclic AMP; monocytes.

Accepted for publication 14 May 1980

Szentivanyi (32) proposed that the manifestations in atopy could be explained by a partial blockade of the beta-adrenergic receptors in the involved cells resulting in imbalanced autonomic nervous system with increased alpha-adrenergic and cholinergic receptor functions. In atopic dermatitis this theory is supported by the clinical findings of white dermographism, decreased digital skin temperature and delayed blanch phenomenon as reviewed in (10). *In vitro* findings of reduced responses to beta-adrenergic stimulation has been reported in skin (6) and peripheral blood granulocytes and lymphocytes (2, 26). In contrast to Busse & Lee (2), Parker et al. (26) showed a decreased response to both isoproterenol and prostaglandin E₁ (PGE₁) suggesting a more general suppression of the

formation of cyclic AMP. Recently, a lowered cAMP response to H₂ histamine receptor stimulation also has been reported in granulocytes (4).

Considerable attention has been focused on the immunological aspects of atopic dermatitis. Abnormal humoral as well as cell-mediated immunity has been reported (7, 21, 29, 33). We previously documented a reduced monocyte function measured as antibody-dependent cell-mediated cytotoxicity (ADCC) in patients with atopic dermatitis (15, 18). There was no evidence for an increased proportion of immature monocytes, depressed Fc receptors or inhibitory serum factors (18). Since the cyclic nucleotides modulate several *in vitro* immune functions including ADCC (9, 11, 34) abnormality of the cyclic AMP

responses might be related to impaired immune functions in atopic dermatitis.

The purpose of the present study was to evaluate if the cAMP responses to various agents were altered in highly purified monocytes from patients with atopic dermatitis and to clarify the relation between cAMP responses and ADCC.

MATERIAL AND METHODS

Subjects

Twenty-one adults with atopic dermatitis were investigated. Their age ranged from 18 to 41 years with an average age of 30 years. There were 13 females and eight males in the group all having cutaneous lesions typical of atopic dermatitis. The patients were graded on a scale 1–5 according to a quantitation of the extent and severity of the disease as earlier described (18, 29). The patients were therefore divided with respect to extent, and in nine patients more than 50% of body area was involved and in 12 patients less than 50%. The product of the grades of the extent and severity in the two groups was 14.3 ± 1.3 and 5.8 ± 0.7 , respectively. In addition to atopic dermatitis six of the patients had a previous history of allergic rhinitis, two of asthma, and four of both allergic rhinitis and asthma.

No systemic treatment was given. Antihistamines were excluded 48 h before examination. No topical steroid more potent than hydrocortisone or hydrocortisone-butyrate was given. Twenty-two control subjects were comparable to the patients with respect to age and sex distribution.

Isolation of monocytes

Isolation of monocytes has been described earlier in detail (16). 150 ml heparinized venous blood was withdrawn from each subject in the study. After Ficoll-Isopaque separation mononuclear cells were allowed to adhere to plastic surfaces. Non-adherent cells were removed by washings and adherent cells

were released by lowering the temperature to 4°C for 30 min. The purity of monocytes was $90.2 \pm 1.5\%$ ($n=43$) as judged by non-specific esterase activity.

Cyclic AMP determinations

Assay for cyclic AMP determinations was made according to Capito & Hedeskov (5) although with some modifications. After isolation, monocytes were resuspended in Hanks' balanced salt solution (HBSS) with 2.5% (v/v) heat-inactivated fetal calf serum (FCS) and adjusted to 15×10^6 /ml. Duplicate samples of 35 μ l were applicated into polypropylene test tubes (Milian Instr., Switzerland). Solutions of either isoproterenol, histamine, or PGE₁ were made in a volume of 7 μ l and the cells were incubated for 5 min at 37°C. Hereafter, 40 μ l of boiling 0.25 M potassiumphosphate buffer (pH 5.5, with 4 mM theophylline and 9 mM 2-mercaptoethanol) were added. The test tubes were immediately immersed in a boiling water bath for 8 min and thereafter kept in an ice bath. Denatured protein was removed by centrifugation (10,000 g for 2 min). Supernatants of 50 μ l were withdrawn and specimens were stored below -20°C until assay was performed. Cyclic AMP was determined by the protein binding competition method using a cAMP assay kit from Radiochemical Centre, Amersham. The samples were counted in Instagel, Packard, on a Tri-Carb scintillation counter. Recovery of a standard solution (1 or 4 pmol cAMP per 50 μ l) after this procedure was $98.5 \pm 4.6\%$ (mean $\pm$ s.e.m., $n=6$) and $94.3 \pm 5.5\%$ (mean $\pm$ s.e.m., $n=6$), respectively, which was comparable to other authors (5).

Monocyte cytotoxicity

The monocyte cytotoxicity assay was performed as earlier described (17). Type B Rh-negative erythrocytes from the same donor were used as target cells throughout the study. The erythrocytes were washed and 150 μ l of cell suspension (2×10^8 /ml) were incubated for 60 min at 37°C with equal volumes of

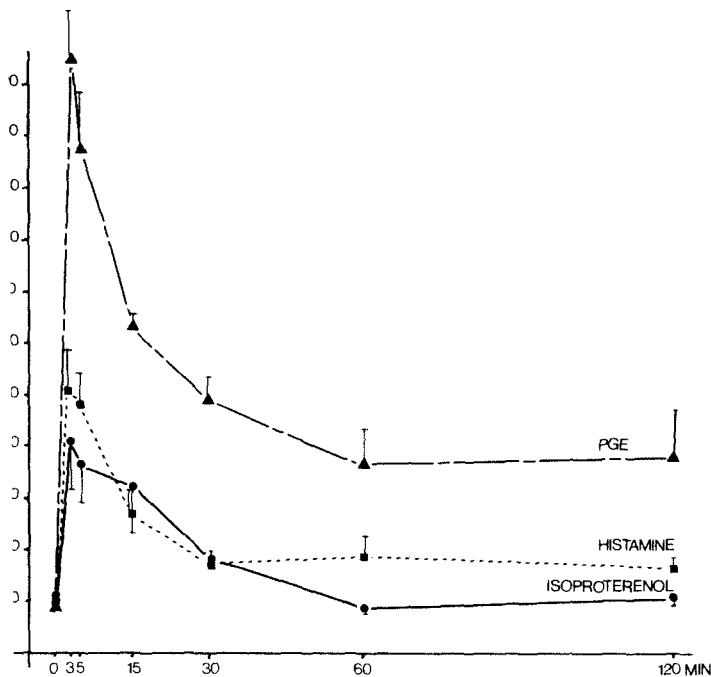


Fig. 1. Cyclic AMP responses in normal monocytes to stimulatory agents as a function of time. At zero time isoproterenol (10^{-5} M), histamine (10^{-4} M), and PGE₁ (3×10^{-5} M) were added to the monocytes. For isoproterenol mean values of seven experiments are presented and for histamine and PGE₁ the values represent the mean of three experiments, respectively.

sodium-⁵¹chromate. Dilutions of monocytes, erythrocytes, and human hyperimmune antiserum to type B human erythrocytes were made in medium RPMI 1640 (including 25 mM Hepes, 2 mM glutamine, 100 IU/ml penicillin, 100 μ g/ml streptomycin, and 5% FCS. In volumes of 100 μ l, monocytes (1×10^6 /ml), ⁵¹Cr-labelled erythrocytes (1×10^6 /ml or 8×10^6 /ml), and 40% antiserum were mixed. In some experiments 30 μ l of isoproterenol, histamine, PGE₁, and dibuturyl-cAMP were added to the mixture of monocytes, erythrocytes, and antiserum. The tubes were centrifuged at 150 g for 1 min and incubated at 37°C for 1 h or 18 h. After incubation the tubes were centrifuged (150 g for 5 min) and half of the supernatant was withdrawn. The chromium release was determined as follows:

$$\frac{\text{supernatant cpm} \times 2}{\text{residues cpm} + \text{supernatant cpm}}$$

Serum IgE

Levels of IgE were quantitated by a radioimmunoassay method (Medicinsk Laboratorium, Copenhagen) considering values above 150 U/ml as pathological.

Materials

Sodium-⁵¹chromate (1mCi/ml, 2–10 μ g Cr/ml) and Cyclic AMP Assay Kit were from Radiochemical Centre, Amersham, England. DL-Isoproterenol-HCl, histamine dihydrochloride, prostaglandin E₁, and N⁶, O²-dibuturyl adenosine 3', 5'-cyclic monophosphate (dibuturyl-cAMP) were from Sigma. Culture medium RPMI 1640 and fetal calf serum were purchased from Gibco (Grand Island, N.Y.). Human hyperimmune antiserum to type B human erythrocytes was obtained from the Blood Bank and Blood Grouping Laboratory, Aarhus Kommune-hospital, Aarhus.

RESULTS

Compared with basal cAMP in purified normal monocytes, additions of isoproterenol, histamine, or PGE₁ increased cellular content of cAMP (Fig. 1). The time-course experiments showed that for each agent maximum levels of cAMP were seen within 3–5 min after addition of agents, followed by a gradual decline. With isoproterenol cAMP concentration reached basal levels after 60 min while histamine and PGE₁, even after 120 min, kept a cAMP level 1.5 and 4 times, respectively, above that for non-stimulated cells. The cAMP response in monocytes after isoproterenol stimulation was inhibited by the beta-adrenergic receptor blocking agent propranolol (not shown). The cAMP response due to histamine was antagonized by the H₂ antihistamine cimetidine but not by the H₁ antihistamine diphenhydramine.

In subsequent experiments cAMP levels in monocytes were measured 5 min after stimulation with different agents. In patients with atopic dermatitis significantly lower

Table 1

Comparison of monocyte cyclic AMP responses in atopic dermatitis and normals

	All patients	Atopic dermatitis		< 50% of skin involved	Healthy controls
		> 50% of skin involved	n		
Buffer	19.2±1.6	21.6±2.4	9	17.4±2.1	21.0±1.3
Isoproterenol	10 ⁻⁵ M	46.5±3.4 ^{**}	21	41.2±4.0\$	50.8±5.3
	10 ⁻⁶ M	33.6±3.0\$	15	32.5±4.0\$	34.4±4.3 ^{**}
Histamine	10 ⁻⁴ M	62.5±7.9 [*]	21	50.5±3.7\$	71.6±13.1
	10 ⁻⁵ M	30.9±2.6\$	15	31.5±3.6 [*]	30.4±5.0 [*]
PGE ₁	3x10 ⁻⁵ M	141.0±14.5	21	118.3±20.0 [*]	158.0±19.7
			9	159.7±11.3	22

Cyclic AMP in monocytes measured 5 min after addition of agents. The values are expressed as picomoles cAMP per 10⁷ cell (mean ± SEM). For statistical evaluation a Mann-Whitney test for two samples was used. P values versus controls. *: p < 0.05, **: p < 0.02, \$: p < 0.01.

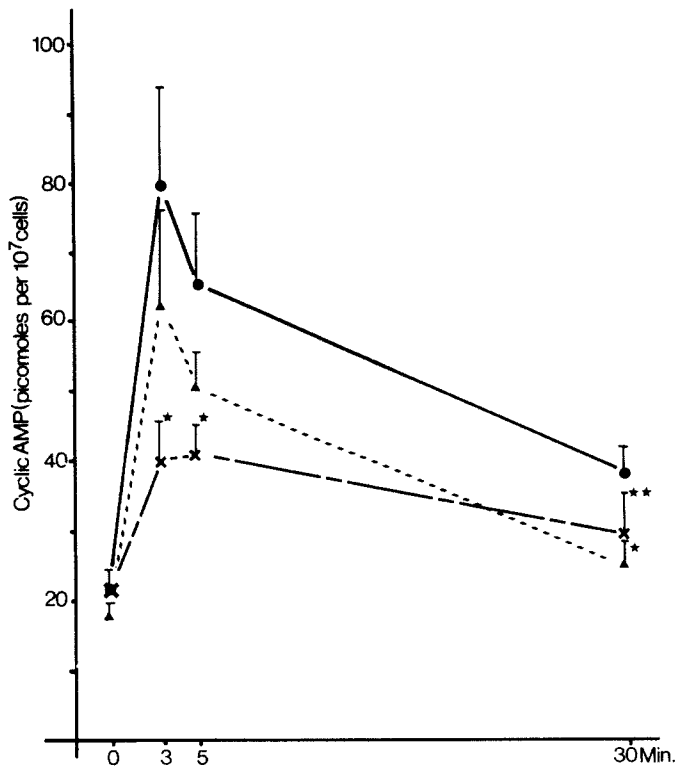


Fig. 2. Monocyte cAMP responses to isoproterenol (10^{-5}M) added at zero time. ●—●: healthy controls ($n=10$). ▲---▲: mild atopic dermatitis ($n=6$). X---X: severe atopic dermatitis ($n=6$). Values are expressed as mean $\pm$ s.e.m. For statistical evaluation a Mann-Whitney test for two samples was used. P values versus controls. *: $P < 0.01$, **: $P < 0.05$.

increase in cellular cAMP after stimulation with 10^{-5}M and 10^{-6}M isoproterenol ($P < 0.02$ and $P < 0.01$, respectively) was obtained (Table 1). Dividing the patients into a mild and a severe group, according to the extent of the disease, the reduced cAMP response was more pronounced in the severe group. Reduced cAMP responsiveness to 10^{-4}M and 10^{-5}M histamine in AD was found in the monocytes. Likewise, patients with severe dermatitis showed more reduced cAMP responses to histamine. Hence, with 10^{-4}M histamine the cAMP response in mild AD was normal. Stimulation with PGE_1 revealed reduced formation of cAMP only in the severe group. Patients with mild dermatitis showed normal cAMP responses to PGE_1 .

Stimulation with isoproterenol (10^{-5}M) showed the same time course for the cAMP response in AD as in controls (Fig. 2). Cyclic AMP content in normal monocytes was constantly above that for atopic dermatitis.

Monocyte ADCC in patients with severe and mild atopic dermatitis is compared with the control group in Table 2. As found earlier (18) the capacity of monocyte function (expressed as the amount of lysis after 18 h) in the presence of target cell excess was significantly reduced in patients with AD ($P < 0.01$). Monocyte ADCC was more reduced, but not significantly, in patients with severe dermatitis (0.94 ± 0.14) than in patients with mild dermatitis (1.23 ± 0.08). There were no differences in cytotoxicity at erythrocyte to monocyte ratio 1:1 after incubation for 1 h.

In addition to the formation of cAMP we looked upon the action of isoproterenol, histamine, and PGE_1 on monocyte function expressed as antibody-dependent cell-mediated cytotoxicity. Experiments were performed at erythrocyte to monocyte ratio 1:1 as patients with AD then express normal ADCC. As shown in Fig. 3 monocyte cytotoxicity is inhibited by agents that increase monocyte cAMP. In severe AD we found a significant correlation between the degree of

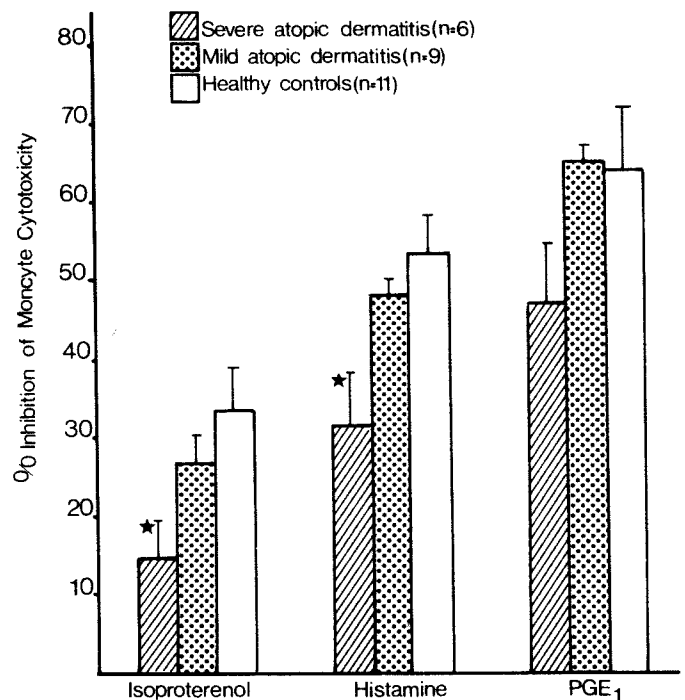


Fig. 3. Inhibition of monocyte cytotoxicity after addition of isoproterenol (10^{-5}M), histamine (10^{-4}M), and PGE_1 ($3 \times 10^{-5}\text{M}$) to the mixture of monocytes, ^{51}Cr -labelled erythrocytes and antiserum. Monocyte to erythrocyte ratio 1:1 and incubation time 1 h. Bars indicate mean $\pm$ s.e.m. For statistical evaluation a Mann-Whitney test for two samples was used. P values versus controls. *: $P < 0.05$.

Table 2

Antibody-dependent monocyte-mediated cytotoxicity in severe and mild atopic dermatitis

Target to effector ratio	1 : 1	8 : 1
Incubation time (h)	1	18
Atopic dermatitis		
All patients (n=21)	0.19 ± 0.02	1.09 ± 0.08*
> 50% of skin involved (n=9)	0.16 ± 0.04	0.94 ± 0.14*
< 50% of skin involved (n=12)	0.20 ± 0.02	1.23 ± 0.08*
Healthy controls (n=22)	0.20 ± 0.02	1.51 ± 0.07

Cytotoxicity is expressed as the mean number of target cells lysed per monocyte ± SEM. For statistical evaluation a Mann-Whitney test for two samples was used. P value versus controls. *: p < 0.01.

inhibition of ADCC and the increase in cAMP with isoproterenol ($P < 0.005$), histamine ($P < 0.005$), but not PGE_1 . In mild AD and in normals, however, we found no close correlation. In patients with severe atopic dermatitis significantly reduced inhibition of ADCC was shown with isoproterenol (10^{-5}M) and histamine (10^{-4}M) to the mixtures, but in the group with mild eczema no differences were seen. PGE_1 inhibited monocyte ADCC slightly in severe atopic dermatitis but not to a level of statistical significance. Addition of 1 mM dibutyl-cAMP induced the same inhibition in normals as in AD ($35.7 \pm 4.5\%$, $n=6$ and $36.7 \pm 5.3\%$, $n=7$, respectively).

All patients with atopic dermatitis had serum IgE levels above normal. There were no significant differences between serum IgE levels in severe and mild atopic dermatitis (3508 ± 1223 , $n=9$, and 1537 ± 352 , $n=12$, respectively).

DISCUSSION

In atopic dermatitis monocytes showed decreased cyclic AMP responses to isoproterenol and histamine, and in severe atopic dermatitis even to PGE_1 . For isoproterenol this was consistent with earlier reports of a relative beta-adrenergic receptor blockade in lymphocytes and granulocytes in atopics (2, 26). Parker et al. (26), in addition, demonstrated a significantly reduced cAMP response to stimulation with PGE_1 in severe but not in mild atopic dermatitis. The recent report of an impaired cAMP response to stimulation of H_2 histamine receptors in active atopic dermatitis complements our findings in monocytes (4). Our results indicate that the defect in cyclic AMP response is not confined to beta-adrenergic stimulation as earlier proposed (2) and a more general suppression of the formation of cAMP in AD is suggested.

Impaired cAMP responses to isoproterenol and histamine have previously been described in asthmatic patients (3, 25). It has been argued, however, that the systemic medications of corticosteroids or adrenergic

drugs may disturb the results. Six of the patients (two with severe and four with mild dermatitis) had a previous history of asthma but none received systemic therapy. In this study the effect of low potent topical steroids seems unlikely to impair monocyte function (24).

In patients with extensive atopic dermatitis a more depressed cAMP response was noted, possibly reflecting the underlying inflammatory process in the skin. Receptor desensitization to isoproterenol and histamine have been described (19, 28) and the reduced cAMP responsiveness could be a result of such a desensitization through mediators of immediate hypersensitivity in the inflammatory process as earlier proposed (26). Inhibition of monocyte function by cutaneous infection can not be excluded, but all our patients were without clinically apparent infections.

We found that in AD monocyte cAMP responses to 10^{-5}M isoproterenol expressed the same time course as in controls, indicating that the choice of incubation time (5 min) was not critical for evaluation of the results. In our preparation we gained a high purity of monocytes (90%) with 1–3% granulocytes, and the rest being lymphocytes. Previously, we showed that lymphocytes are not effector cells in our ADCC assay (17) and no interference was observed. Purified lymphocytes contain 30.7 ± 1.6 pmol cAMP per 10^7 cells ($n=7$). Preliminary experiments show that the hormonal cAMP responsiveness was approximately 25% above that for monocytes, indicating that lymphocytes contribute only minimally to the cAMP responses in monocytes.

It has not been possible to localize the defect of beta-adrenergic receptor stimulation further. Increased phosphodiesterase activity in leukocytes would tend to lower cAMP content but this seems unlikely as incubation with theophylline induced significantly lower cAMP values in severe atopic dermatitis (26), and investigations of the skin have showed normal phosphodiesterase (13) in atopics. Also

adenyl cyclase in skin (22) was within normal range. Galant et al. (8) showed that the number of beta-adrenergic receptors on leukocytes was normal in AD indicating that the defect cAMP responses may be beyond the hormone-receptor site. It has been proposed that the coupling of hormone-receptor with membrane-bound adenylyl cyclase is disturbed (8).

In monocytes histamine mediates the formation of cAMP through an activation of H₂ histamine receptors, also demonstrated in granulocytes and lymphocytes (4, 20). In mast cells and basophilic leukocytes antigenic histamine release is inhibited by H₂ receptor stimulation (1). If the impaired cAMP responses to histamine are also present in mast cells or basophils an enhanced release of histamine in AD could be conceivable. Increased histamine concentration in skin has been demonstrated (14, 23) but because of great individual and regional variation in skin the results were not conclusive. Urinary excretion of histamine in atopic dermatitis is not increased (27). On the other hand, lymphocyte transformation to phytohemagglutinin stimulation can be inhibited by agents including histamine that increase cAMP (30). However, lymphocytes from AD patients have shown increased sensitivity to histamine-induced suppression of lymphocyte reactivity (31). From this the role of histamine in the pathogenesis of atopic dermatitis still seems unclear to us.

Isoproterenol, histamine, and PGE₁ inhibit monocyte cytotoxicity corresponding to the concomitant rise in cAMP levels as described for other cytotoxicity assays (9, 11). Inhibition of cytotoxicity was relatively insensitive to isoproterenol (10⁻⁵M) and histamine (10⁻⁵M), but not to PGE₁, in severe AD. If the modulation of cAMP is responsible for monocyte cytotoxicity one would expect an enhanced monocyte cytotoxicity in AD. These results seem therefore to conflict with our findings of a depressed monocyte cytotoxicity in AD. However, in polymorphonuclear leukocytes stimulation with dialyzed latex

particles phagocytosis is initiated by a short and reversible increase in cAMP (12). Whether initiation of monocyte cytotoxicity is similarly dependent on an initial cAMP response is still under investigation. Possibly, the relation of depressed monocyte cytotoxicity to defects in cyclic nucleotide regulation in AD might show a shared abnormality at the membrane site.

ACKNOWLEDGEMENTS

We are indebted to the Department of Pathology, Amtssygehuset, Aarhus, for performing the esterase staining of monocytes. We wish to thank Mrs Winnie Heidemann for expert technical assistance. This work was supported by the Danish Medical Research Council grant No. 512-20089.

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