Acta Derm Venereol (Stockh) 1985; Suppl. 114: 9–23

Altered Releasability of Vasoactive Mediator Secreting Cells in Atopic Eczema

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A summarizing survey of different studies in atopic eczema involving three types of cells (platelets, neutrophils, basophils) and their mediators is given. *Platelets* were found to release normal amounts of serotonin upon stimulation with epinephrine, thrombin and slightly reduced amounts after aggregated IgG stimulation. Serotonin uptake by washed platelets was found to be slower in atopics than in normals. *Neutrophils* showed a decreased release of β-glucuronidase to stimuli like zymosan or aggregated IgG in atopics compared to controls. This might be regarded as a contributory factor to the well-known decreased resistance to infections observed in atopic eczema. *Basophils* in most studies released increased amounts of histamine in the atopic population compared to controls, especially after stimulation with anti-IgE. Concomitantly to the histamine release there was a slight increase in prostaglandin E2 production both in atopics and normals, which was increased by preincubation with reduced glutathion—a coenzyme of PGE2 isomerase. Histamine release tended to occur faster in atopics. Two possible factors influencing releasability characteristics were studied, namely the cyclic nucleotide system and arachidonic acid (AA) dependent mechanisms. Leucocytes of atopics showed a decreased response of cAMP to β-adrenergic and an increased response of cGMP to cholinergic stimulation. Significant augmentation of anti-IgE-induced histamine release was observed after cholinergic stimulation. AA metabolites obviously play a regulating role in mediator release. PGE2 inhibited histamine release to various stimuli both in atopics and in normals. Indomethacin enhanced histamine release, especially after anti-IgE stimulation in atopics, while it inhibited complement-dependent release reactions both in atopics and in normals. The exogenous inhibitors of lipoxygenase eicosatetraynoic acid (ETYA) and nordihydroguaretic acid (NDGA) inhibited histamine release equally in atopics and normals. The endogenous lipoxygenase inhibitor 15-HETE showed no inhibitory but rather a slight enhancing effect upon histamine release. It is concluded that patients with atopic eczema often exhibit altered releasability patterns to a variety of stimuli. On the basis of our findings we describe "altered releasability" as one factor of a *vicious cycle* between increased IgE-production, mediator secretion and T cell regulatory disturbances in the pathogenesis of atopic eczema.

Releasability is defined as the capacity of mediator secreting cells to release preformed or newly synthetized mediators (15, 47, 71). Histamine is one of the best studied substances, and the best established mechanism is the IgE-mediated reaction (7, 36, 83). There are, however, other stimuli and other mediators of possible clinical importance, like Ca-ionophore, complement C5a, and other direct histamine liberators (22, 46, 47, 50). During the last few years numerous studies have been performed dealing with altered releasability characteristics in atopic diseases. Here we try to present a summarizing survey of different studies in patients with atopic eczema, mainly focusing on work performed by our group. These studies involve three types of cells and their mediators, namely basophils (histamine), neutrophils (β-glucuronidase) and platelets (serotonin). If not mentioned otherwise, the patients of the here presented studies were selected according to diagnostic criteria corresponding to those of Hanifin & Rajka (31, 56). For detailed information regarding materials and methodology, the reader is referred to the original publications.

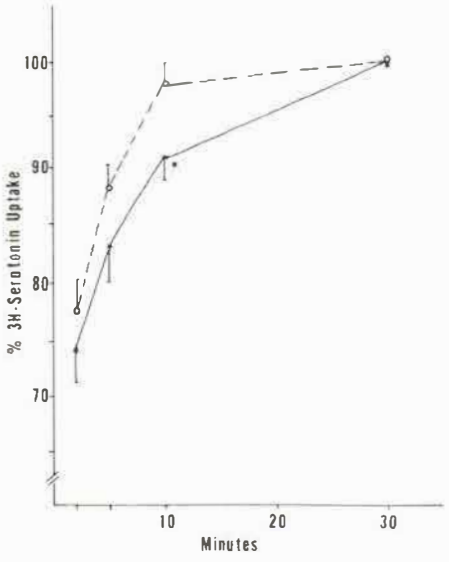

Fig. 1. In vitro uptake (mean values ± SEM) of 3H serotonin by platelets from atopic patients ($n=16$) and normal controls ($n=9$). *$p<0.05$ (from 66a).

Platelets and serotonin release

Washed peripheral blood platelets of patients with atopic eczema wree found to release normal amounts of serotonin after stimulation with epinephrine, thrombin, Ca-ionophore, and slightly reduced amounts after aggregated IgG stimulation (Table I). When platelets where incubated with radiolabelled serotonin, the uptake of serotonin was found to occur significantly slower in atopics (Fig. 1) then in normals (66). At present this finding remains unexplained; however, it is of interest that similar data have been reported from depressive patients with and without systemic therapy with tricyclic antidepressive drugs (4, 45). At the time of investigation, none of our patients had taken such drugs. Subpopulations of platelets with lower density, probably representing "older" platelets were shown to take up serotonin at a lower rate than "young" heavy platelets (4).

Little is known about the role of platelets in atopic diseases. Some authors described increased platelet activation in bronchial asthma (48). Recently a platelet-derived factor enhancing histamine release from basophils was described (42). A cyclic platelet dysfunction was reported in hay-fever patients during pollen season (25).

In some patients increased plasma serotonin concentrations (ranging from 3.3–10 ng/ml)

Table I. *In vitro and in vivo studies of serotonin release in atopic eczema (from 65, 66, 71)*

In vitro serotonin release	
Thrombin	Normal
Ca-ionophore	Normal
Epinephrine	Normal
Aggregated IgG	Decreased
In vitro serotonin uptake	
Decreased	
In vivo serotonin plasma concentrations	
Elevated in 8/23 patients (3.3–10.0 ng/ml)	

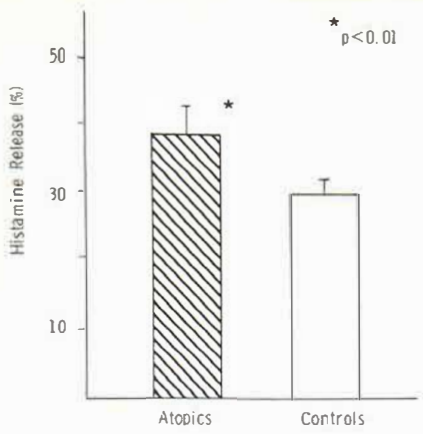

Fig. 2. Five minutes after stimulation with anti-IgE (Behring-Werke, Marburg, dilution 1 : 1000) leucocytes of atopic patients release significantly more histamine than controls (from 91).

where detected without correlation to the clinical severity (Table I). Decreased total serotonin contents of platelets have been found in autoimmune diseases (96).

Role of complement in atopic eczema

Table II summarizes data from the literature on complement activation in atopic eczema (26, 41, 62, 63, 80, 93, 95). We have observed patterns of decreased functional complement activity for certain complement components like C3H50, C2H50 (63) as well as deposits of complement factors (mostly C3) and immunoglobulins in involved and uninvolved skin of patients with atopic eczema in a granular pattern at the dermo-epidermal junction (62).

Neutrophils and lysosomal enzyme release

Lysosomal enzyme release was investigated using various stimuli for neutrophil leukocytes and measuring β-glucuronidase (β-glu) as a lysosomal enzyme and lactate dehydrogenase (LDH) as a cytoplasmic enzyme and a marker of cellular lysis. We found decreased release rates of β-glu after stimulation with activated complement C5a, zymosan, aggregated IgG as well as antilymphocyte globulin in patients with severe atopic eczema (68). There was an indirect correlation between the lysosomal enzyme release and the intensity of the skin lesions. These findings were interpreted as a possible contributory factor—similar to decreased leukocyte and monocyte chemotaxis described by others (30)—to the well-known decreased resistance to infections observed in this disease (56, 79, 94).

Table II. *Studies on complement changes in atopic eczema*

Data	Authors	Year
Normal or increased C3	Kaufman et al.	1968
Normal or increased C3	Wüthrich et al.	1972
Decreased CH50	Yamamoto	1975
Ig and C deposits in skin	Ring et al.	1978
Decreased CH50, C3H50 and C2H50	Ring et al.	1979
Defective alternate pathway activation, functional C2 deficiency	Gianetti	1980
Increased C3, C4 and C1-INA	Schöpf et al.	1984

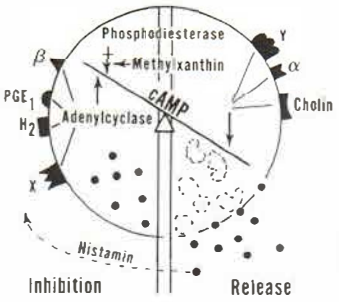

Fig. 3. Schematic presentation of "balance" of intracellular cAMP showing different stimuli inhibiting or enhancing histamine release (from 64).

Basophil leucocytes and histamine release

Histamin release from washed peripheral leucocytes was measured spectrofluorometrically according to the method of Siraganian (83) after in vitro stimulation with various stimuli. In the various studies performed by our group, basophil leucocytes mostly—although not generally—released increased amounts of histamine in patients with atopic eczema compared to controls after stimulation with anti-IgE. Nowhere in all our studies did this difference reach statistical significance. Similar findings of altered histamine releasability in atopic patients have been reported by others (5, 14, 89), although, in a study in patients with atopic rhinitis and asthma, we found decreased rates of anti-IgE-induced histamine release (6a).

It was of special interest that in kinetic studies, the speed of the release reaction in the first five minutes was significantly faster in atopics compared to controls (Fig. 2) (Von der Helm, Ring, Dorsch, in prep.). This might be of possible clinical relevance with regard to an increased local concentration of vasoactive mediators after initiation of a release reaction.

In order to investigate factors regulating basophil releasability two systems were studied, namely 1) the influence of autonomic nervous system mediators together with cyclic nucleotides and 2) arachidonic acid metabolites.

Cyclic nucleotide metabolism and histamine release in atopic eczema

For decades and particularly since the first description of the theory of β-adrenergic blockade as possible explanation for the atopic abnormality in bronchial asthma by

Table III. *Altered in vitro leucocyte cyclic nucleotide responsiveness in atopic eczema*

Stimulus	Nucleotide	Response	Authors	Year
β-Angonist	cAMP	Decreased	Parker et al.	1973
PGE_1	cAMP	Decreased	Parker et al.	1973
β-Agonist	cAMP	Decreased	Reed et al.	1976
PGE_1	cAMP	Normal	Russe, Lee	1976
Histamine (H_2 effect)	cAMP	Decreased	Busse, Lantis	1976
β-Agonist	cAMP	Decreased	Ring et al.	1981
Methycholine	cGMP	Increased	Ring et al.	1981
β-Agonist	cAMP	Decreased	Archer et al.	1983
PGE_2	cAMP	Decreased	Archer et al.	1983
Decreased affinity of *b*-adrenergic receptor			Pochet et al.	1980
Increased cAMP phosphodiesterase activity			Hanifin	1983
Increased cAMP in atopic neonates			Heskel et al.	1983

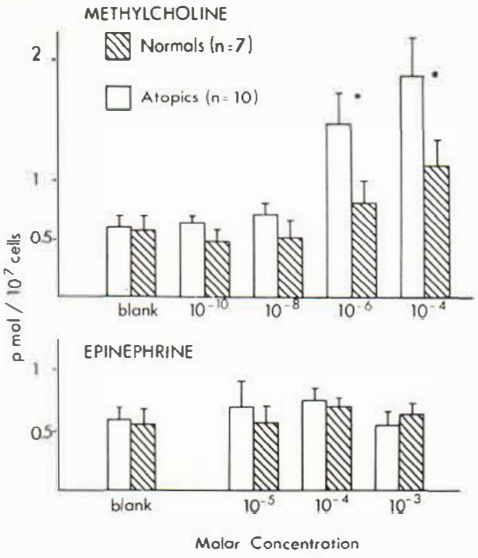

Fig. 4. Changes in intracellular cyclic guanosin-monophosphate (cGMP) concentrations after in vitro stimulation with methylcholine and epinephrine in different concentrations in patients suffering from atopic eczema and normal controls. There was a significantly greater increase in cGMP in atopics after methylcholine stimulation compared to normals (from 6b).

Szentivanyi (87) numerous authors have put forward the concept of a dysregulation of autonomic nervous system (39, 43, 44) and cyclic nucleotide reactivity (Fig. 3) in patients with atopic eczema (Table III) (2, 12, 13, 27, 32, 40, 54, 55, 59, 67, 90). The impaired β-adrenergic reactivity together with reduced cAMP responses of peripheral leucocytes might be explained by the findings of Hanifin and coworkers who described elevated levels of the cAMP inactivating enzyme phosphodiesterase in leucocytes of patients with atopic eczema (14, 29, 32, 34, 77), this marker already being present in neonates (34). Other explanations might be autoantibodies against the β-receptor (9) or a decreased receptor affinity (55, 88).

Together with the decreased response of cAMP to β-adrenergic stimuli in vitro we observed an increased response of cGMP to cholinergic stimulation (Fig. 4) (67).

There are controversial data regarding the effect of cholinergic stimulation upon histamine release from mast cells and basophils in different species (21, 40, 65, 74, 86). We

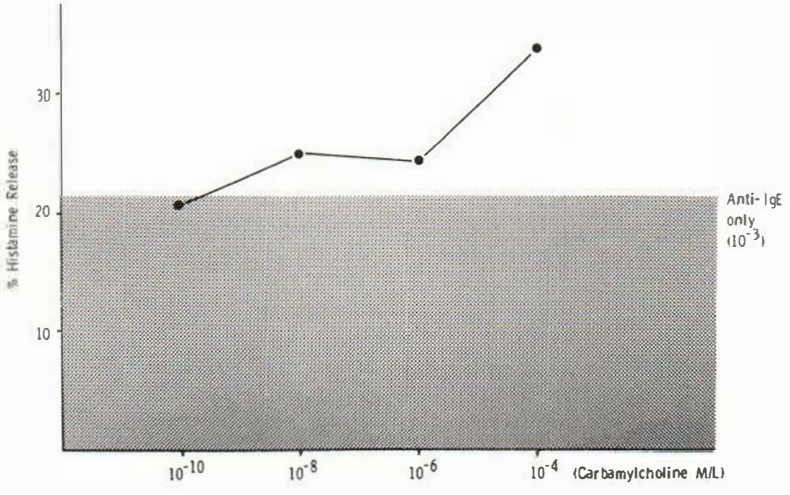

Fig. 5. In vitro addition of carbamylcholine significantly enhances anti-IgE-induced histamine release; typical example of a patient with atopic eczema (Ring, Sedlmair, in preparation).

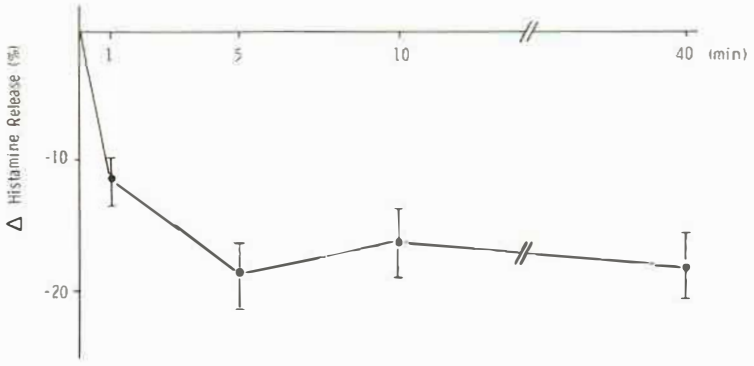

Fig. 6. Addition of PGE2 significantly inhibits anti-IgE-induced histamine release from peripheral leukocytes (from 91).

found significant augmentation of anti-IgE-induced histamine release from basophils after incubation with carbamylcholine (Fig. 5) which seemed to be more pronounced in atopics than in controls.

These in vitro observations of autonomic mediator dysregulation are supported by in vivo studies (1, 33, 49) showing e.g. increased responses of pupillary constriction or blood pressure to α-adrenergic and cholinergic stimulation in atopics (33); others found no difference in the skin reactivity of patients with atopic eczema to α- and β-adrenergic antagonists (3).

The here presented findings of disturbances of autonomic nervous system mediators influencing histamine release might be important with regard to the well-known clinical influence of psychosomatic interactions familiar to all dermatologists (10, 92). It might be of interest in this context that stress per se is able to induce histamine release in animals and humans (60) as shown e.g. during a minor dental therapeutic procedure (Ring, in preparation).

Arachidonic acid metabolism and histamine release

Arachidonic acid metabolites obviously play a regulating role in mediator release (7, 50, 76, 91). The precise role of single products of the cyclooxygenase or lipoxygenase pathway, however, in different pathological conditions is not yet established.

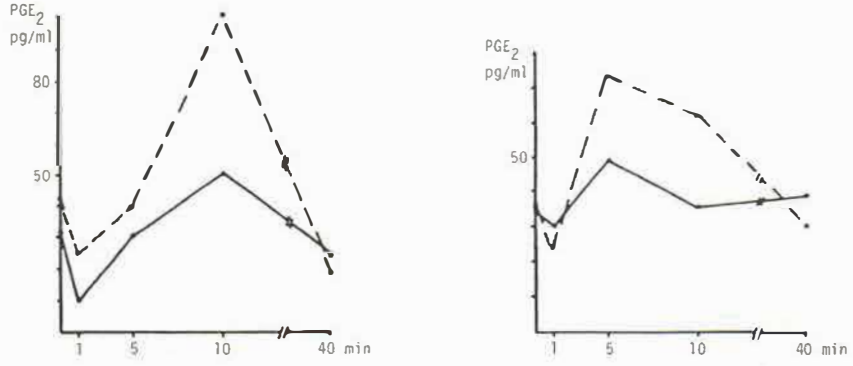

Fig. 7. After anti-IgE-stimulation of peripheral leukocytes there is a slight increase in PGE2 concentration in the supernatant. By addition of reduced glutathione (GSH) (dotted line) these PGE2 concentrations are significantly enhanced. The PGE2 production occurred markedly slower in atopics (typical example of an atopic patient left) compared to controls (right) (Ring, von der Helm, Dorsch, in preparation).

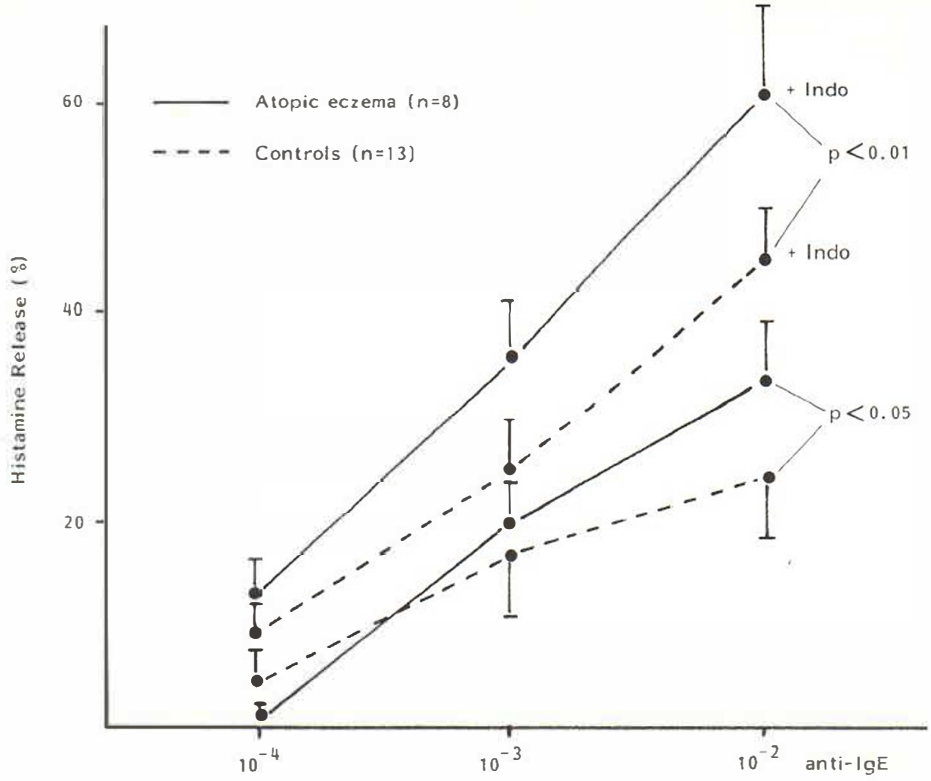

Fig 8. In vitro histamine release from peripheral leucocytes after stimulation with anti-IgE is significantly increased in atopics compared to controls. By addition of indomethacin (10^5 M) this reaction is further enhanced both in atopics and in controls (Ring, Walz, in preparation).

Cyclooxygenase products

Among the prostaglandins, PGE2 inhibits histamine release after various stimulators in atopics and normals, when added exogenously (Fig. 6) (50, 91) Concomitantly to the anti-IgE-induced histamine release we observed a slight increase in PGE2 production by the leukocyte suspension. This endogenous PGE2 production was increased after preincubation with reduced glutathion---a coenzyme of PGE2 isomerase. Again, there were differences in the speed of the reaction: glutathion-induced PGE2 increase was slower in atopic patients compared to normal individuals (Von der Helm, Ring, Dorsch, in preparation) (Fig. 7).

On the other hand, cyclooxygenase inhibitors like acetylsalicylic acid (ASA) or indomethacin enhanced histamine release, especially after anti-IgE stimulation (Fig. 8). This enhancement was significantly more pronounced in patients with atopic eczema compared to controls. In this particular experiment patients with allergic rhinitis and/or asthma alone as well as patients with urticaria showed similar values as non-atopic controls (Ring, Walz, in preparation).

While indomethacin tended to enhance considerably histamine release towards a variety of stimuli, there was a clear inhibition of C5a-induced histamine release reactions both in atopics and normals. This might be of interest for therapeutic considerations in complement-dependent diseases as e.g. urticaria vasculitis (52). It becomes clear from these findings that releasability is not a single parameter but has to be evaluated differently for different stimuli!

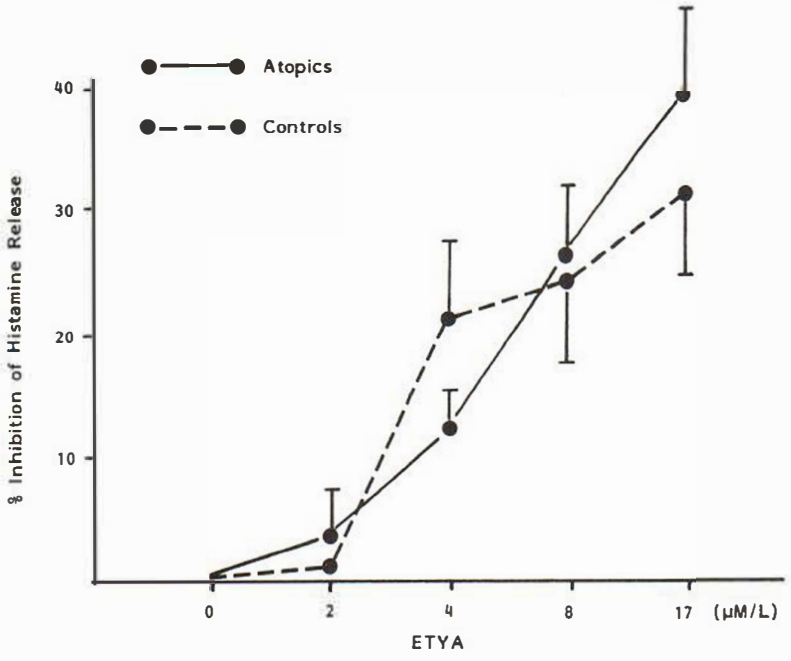

Fig. 9. Addition of eicosatetraynoic acid (ETYA) strongly inhibits anti-IgE-induced histamine release from peripheral leukocytes both in atopics and controls (adapted from 19).

Lipoxygenase inhibitors and histamine release

The exogenous addition of inhibitors of lipoxygenase-like eicosatetraynoic acid (ETYA) and nordihydroguaretic acid (NDGA) inhibited histamine release in a dose-dependent manner equally in atopics and normals (Fig. 9). The endogenous lipoxygenase inhibitor 15-hydroxyeikosatetraenoic acid (15-HETE), however, showed no inhibitory effect upon

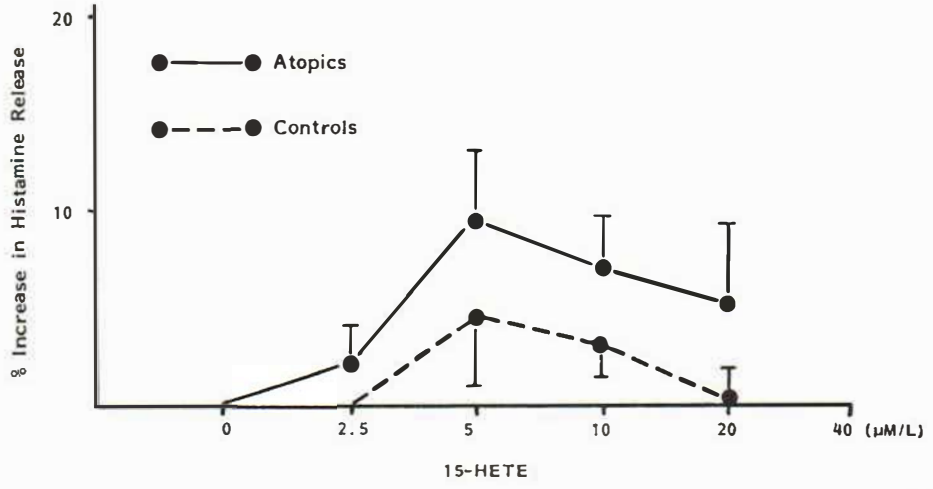

Fig. 10. 15-hydroxyeicosatetraenoic acid (15-HETE) shows a slight enhancing effect upon anti-IgE-induced histamine release in atopics. This was in contrast to the expected finding of inhibition of histamine release by lipoxygenaseblockers (15-HETE has been described as lipoxygenaseblocker in human cells).

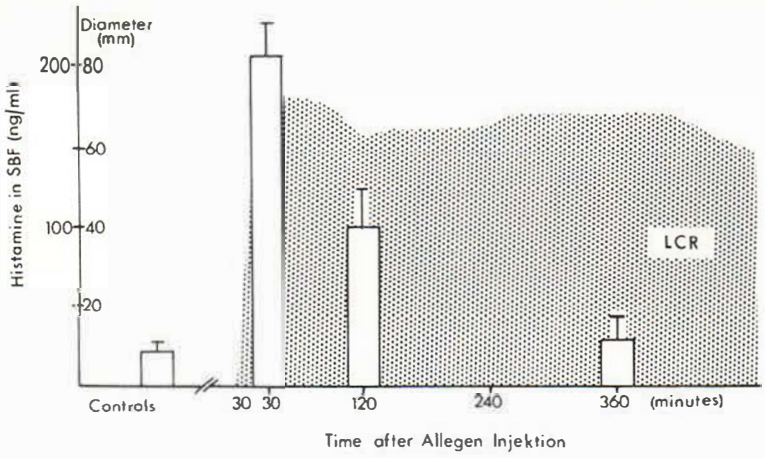

Fig. 11. Concentrations of histamine in skin blister fluid (SBF) drawn over late cutaneous reactions (LCR) (diameter shown as shaded area) over the development of LCR and compared to SBF over control skin (adapted from 17).

histamine release reactions; on the contrary there was a slight enhancing effect on histamine release, which was clearly more pronounced in the atopic population (Fig. 10) (19).

In vivo studies

Looking at all this in vitro work one wants to know, whether this has some relevance in vivo. Indeed, we were able to find increased plasma histamine concentrations in patients with severe eczema (69) using a radioenzymatic assay (8) similarly to results in patients with asthma (82). When we followed the clinical course of these patients, however, elevated histamine levels returned to normal during phases of remission. First clinical trials using H_1 and H_2 antihistamines were not too promising (11, 24, 58).

Increased concentrations of various mediators have been found in atopic skin by some authors while others found normal values (37, 38, 51, 53, 63, 69, 74) (Table IV). Of particular interest in this context might be the elevated values of leukotriene LTB4 in involved skin of patients with atopic eczema (16, 75). However, similar elevations of LTB_4 concentrations have been found in psoriasis and bullous pemphigoid (16).

By several authors late cutaneous reactions (LCR) are regarded as a possible model to study the pathophysiology of events leading to longlasting asthmatic conditions or atopic eczema (7, 17, 71). Therefore the question of the relevant mediators of LCR is of great interest in this context. Studies performed by Dorsch et al. demonstrated elevated histamine concentrations in skin blister fluid 30 min after allergen testing and decreasing towards normal in spite of ongoing LCR (Fig. 11) (17). In some blister fluids, kinin activity

Table IV. *Histamine concentrations in tissue and plasma in atopic eczema*

Elevated skin histamine levels	Johnson et al.	1960
Elevated skin histamine levels	Juhlin	1967
Increased mast cell numbers	Mikhael, Miller-Milenska	1976
Increased mast cell numbers	Mihm et al.	1976
Normal skin histamine levels	Ruzicka, Glück	1980
Elevated plasma histamine concentrations	Ring et al.	1979
Elevated plasma histamine concentrations (normal during remission)	Ring	1983

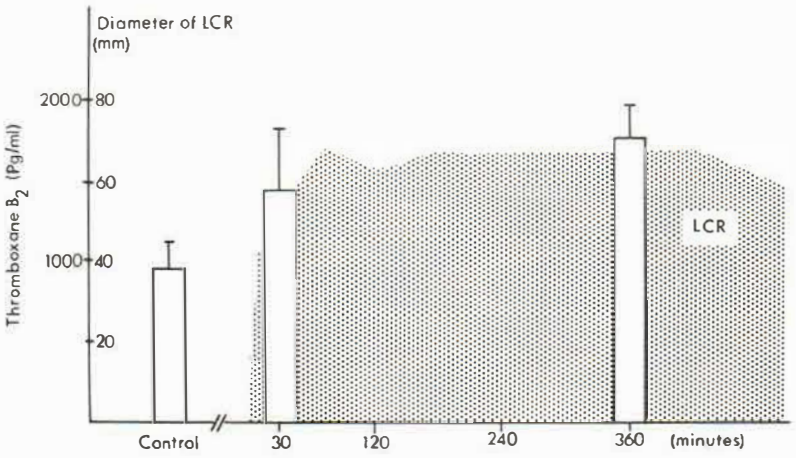

Fig. 12. Thromboxane B2 concentrations of histamine in skin blister fluid (SBF) drawn over late cutaneous reactions (LCR) (diameter shown as shaded area) over the development of LCR and compared to SBF over control skin (adapted from 17).

was demonstrable; thromboxane B2 was one mediator showing no decrease but rather an increase over 6 hours of LCR formation in skin blister fluid (Fig. 12). In a clinical study in volunteers it could be shown that pretreatment with a thromboxane biosynthesis inhibitor like dazoxibene was able to reduce the intensity of LCR, while immediate wheal and flare reactions were enhanced (18). Recently immunoreactive leukotriene LTC4/D4 was demon-

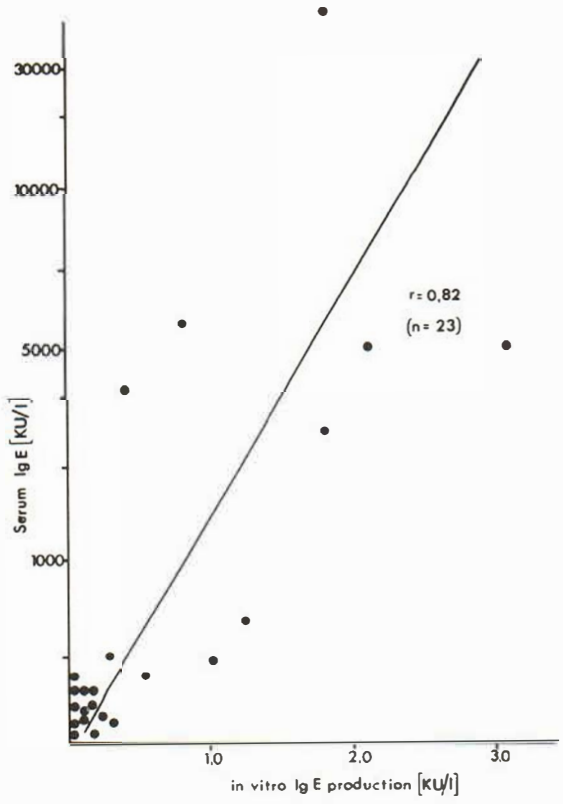

Fig. 13. Correlation between spontaneous in vitro-IgE-production from peripheral leucocytes to serum-IgE levels in patients with atopic eczema (from 70).

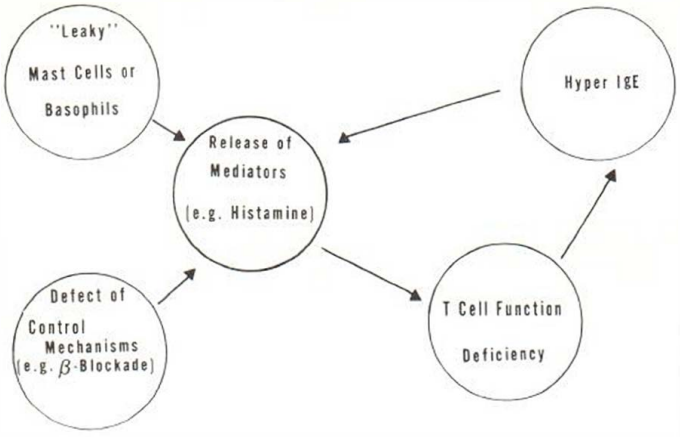

Fig. 14. Vicious cycle of different factors (increased IgE-production, altered releasability, T-cell regulatory disturbances) in the pathogenesis of atopic eczema (from 61).

strated in significantly higher amounts in skin blister fluid over LCR after allergen testing compared to control skin (20).

Lymphocyte in vitro IgE-secretion

From a point of view, in vitro IgE-secretion by peripheral lymphocytes might be considered as a form of "releasability" of peripheral leukocytes too. Various authors have provided data about increased spontaneous in vitro IgE-secretion in patients with atopic eczema (23, 35, 70). Our own data are in accordance with these findings. Furthermore we were able to show a significant positive correlation between serum IgE and in vitro IgE-secretion (Fig. 13). By now, the mechanisms of regulation of IgE-synthesis in man are not well established, although much is known about IgE-regulation in rodents (35). It is generally assumed that isotype specific suppressor and helper T-cells play an important role (35). The relevant subpopulation (perhaps Fcε-receptor bearing lymphocytes (84), however, is not known at the moment. Furthermore, the exact pathogenetic role of IgE-reactions in atopic eczema is still controversial (5, 32, 56, 57, 94).

Conclusions

It is concluded that patients with atopic eczema often exhibit altered releasability patterns of mediator secreting cells to a variety of stimuli. The observed changes do not seem to be consisting "defects", since they often change in the same individual during different clinical stages of the disease. At present, we cannot explain the mechanism of this altered releasability in our patients.

It has to be very carefully distinguished between different cells, different stimuli, different modulating agents and different manifestations of the atopic abnormality when discussing the problem of mediator releasability.

Many of the substances discussed in this context—like e.g. histamine or PGE2—not only act as vasoactive mediators promoting inflammatory symptoms but exert regulatory functions mostly in an inhibitory sense via specific receptors at the lymphocyte level (9, 72, 73, 81, 85).

On the basis of our findings we describe "altered releasability" as one factor of a vicious cycle (Fig. 14) between increased IgE production, mediator secretion and T cell regulatory disturbances in the pathogenesis of atopic eczema.

ACKNOWLEDGEMENT

The authors want to thank Ms Fransziska Beier for the excellent technical assistance provided over the last few years.

This work was supported by grant Ri 307/6 from the Deutsche Forschungsgemeinschaft.

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