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Histamine and Atopic Eczema

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Apart from increased production of immunoglobulin E antibodies and disturbed T-cell regulation, altered patterns of releasability of vasoactive mediators have been described in patients with atopic exzema. The best studied substance is histamine which is a classical inducer of pruritus in man. Elevated concentrations of histamine have been found in vivo in the skin and in the plasma of patients with atopic exzema especially during exacerbation of the disease. Similar findings have been described for other atopic diseases as extrinsic bronchial asthma. Histamine acts via characteristic receptors; symptoms as itch, wheal formation, mucus production, contraction of smooth muscle, tachycardia and hypotension are mediated via H1-receptors, while H2-effects include acid secretion in the stomach as well as the development of flush and itch reactions, blood pressure changes and cardiac arrhythmia. Of special interest is an inhibitory effect of histamine on lymphocyte reactions mediated via a H2-receptor. The existence of a new H3-receptor in the brain serving as autocrine feed-back inhibitor of histaminergic neurones has been established in the rat but not yet in man. In vitro an increased histamine releasability of peripheral leukocytes has been found after stimulation with a variety of different substances. The difference between patients with atopic eczema and normals is generally most pronounced after stimulation with anti-IgE. There is, however, a tendency towards an increased spontaneous histamine release compared to normals. The release reaction of histamine seems to occur more rapidly in atopics compared to normals. Among possible factors influencing histamine releasability the imbalance in the cyclic nucleotide system (increased response of cGMP to cholinergic stimulation and decreased response of cAMP to β-adrenergic stimulation) might play a pathogenetic role. Arachidonic acid metabolites known to regulate histamine release (PGE_2 inhibits histamine release while cyclooxygenase blockers enhance histamine release and lipoxygenase blockers inhibits histamine release) also may be of relevance. Histamine definitely is not the only relevant mediator substance in the pathophysiology of atopic eczema; it may, however, serve as a marker of mast cell and basophil activation. Clinical trials with various antihistamines have shown some therapeutic benefit in the management of atopic eczema patients. Future studies in the field of mediator research may lead to new therapeutic approaches for the treatment of atopic eczema.

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HISTAMINE EFFECTS

Although known for almost 80 years, histamine still remains a fascinating substance for many researchers (7, 8, 17, 18, 28, 46, 47, 53, 69, 83). The definition of the physiological role of histamine in health and disease remains incomplete. We know that histamine exerts powerful effects mainly via two receptors (Table I). The description of a new H3-receptor in the brain deserves special interest (4, 81 *a*).

The role of histamine as a mediator of immediate-type hypersensitivity diseases (both allergic and pseudo-allergic in origin) is quite well established (7, 16, 17, 36, 68, 79). Similarly well defined is the H2-mediated role of histamine in the induction of gastric acid secretion.

Recent interest has focussed on anti-inflammatory effects of histamine as a modulator of immune reactions acting predominantly on H2-receptors on the surface of leukocytes there by inhibiting a variety of immune reactions (Table II) (9, 13, 72, 73, 81, 85).

In a study in 16 patients with atopic eczema we found an inhibitory effect of histamine upon pokeweed-mitogen(PWM)-induced lymphocyte stimulation (Fig. 1). This effect was shown to depend upon the presence of T8-lymphocytes in the cell suspension, a shown in Fig. 2: after depletion of T8-lymphocytes the inhibitory effect of histamine upon PWM-induced lymphocyte stimulation was no longer demonstrable in atopics nor in controls.

Role of histamine in the pathophysiology of atopic eczema

In spite of great progress in experimental and clinical allergology and dermatology in the last decades the

Table I. *Histamine effects in human organs*

Organ	Stimulatory	Inhibitory	None/ negligible
Vessels			
Large veins (>80 μm)	+	–	–
Arterioles, venules (20–30 μm)	–	+	–
Permeability of "capillaries" (postcapillary venules)	+	–	–
Extravascular smooth muscle			
Bronchi, gut	+	–	–
Uterus, bladder, gallbladder, iris	–	–	+
Stomach (secretion)	+	–	–
Salivary glands	+	–	–
Heart			
Rate, force, output	+	–	–
AV conduction	–	+	–
Ventricular arrhythmia	+	–	–
Nervous system			
Sensory fibers	+	–	–
Central effects	(+)?	–	–
Endocrine system			
Adrenal medulla	–	–	+
Leukocytes	–	+	–

pathogenesis of atopic eczema is still not well established.

Research interest has focussed on mainly three aspects:

increased production of immunoglobulin E,

disturbed T-cell regulation,

altered pharmacological reactivity and releasability of vasoactive mediators (6, 11, 15, 23, 25, 26, 31, 32, 35, 41, 42, 43, 44, 48, 56, 57, 58, 62, 63, 80, 85, 94).

Previously we have advanced the concept of a "vicious cycle" of this different factors acting together in the pathophysiology of atopic eczema (61).

The best studied mediator substance is histamine which is a classical inducer of pruritus in man (57, 69). Elevated concentrations of histamine have been found in vivo in the skin and in the plasma of patients with atopic eczema especially during exacerbation of the disease (37, 38, 66, 74) (Table III). Similar findings have been described for other atopic diseases as extrinsic bronchial asthma (82). In vitro an increased histamine releasability of peripheral leukocytes has been found after stimulation with a variety of different substances by many other authors (5, 14, 15, 22, 51, 65, 69, 74, 90). The difference between patients with atopic eczema and normals is generally most pronounced after stimulation with anti-IgE. There is, however, a tendency towards an increased spontaneous histamine release compared to normals (69, 84). The release reaction of histamine seems to occur more rapidly in atopics compared to normals (91).

Among possible factors influencing histamine releasability the imbalance in the cyclic nucleotide system (increased response of cGMP to cholinergic stim-

Table II. *Immune reactions inhibited by histamine*

Mast cells and basophils (mediator release)
Neutrophil function (chemotaxis, phagocytosis, enzyme release)
Eosinophils
Macrophages (complement production)
Lymphocyte proliferation and lymphokine production
Lymphocyte cytotoxicity
Concanavalin A-induced suppressor cell activity

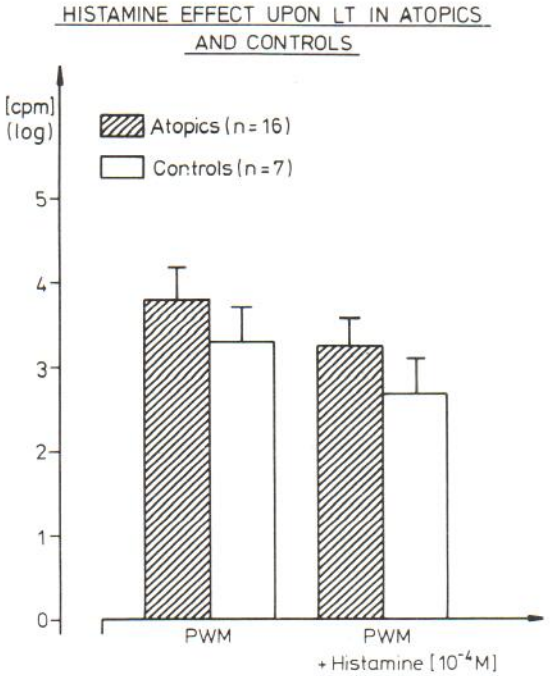

Fig. 1. Effect of histamine added to lymphocyte cultures upon lymphocyte transformation (LT) induced by pokeweed mitogen (PWM) in patients with atopic eczema and controls.

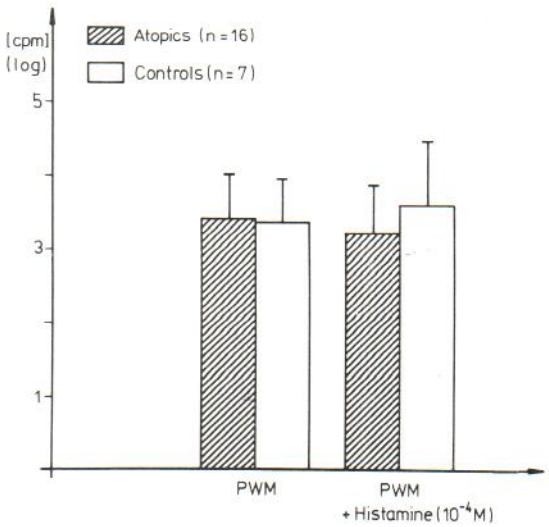

Fig. 2. Effect of histamine added to lymphocyte cultures upon lymphocyte transformation (LT) induced by pokeweed mitogen (PWM) in patients with atopic eczema and controls after specific depletion of T8-cells by rosetting technique with monoclonal antibodies (see ...)

ulation and decreased response of cAMP to β-adrenergic stimulation) (1, 3, 12, 14, 21, 27, 34, 40, 43, 49, 54, 59, 64, 65, 78, 86, 87, 88) might play a pathogenetic role.

Arachidonic acid metabolites known to regulate histamine release (PGE_2 inhibits histamine release while cyclooxygenase blockers enhance histamine release and lipoxygenase blockers inhibits histamine release) (2, 16, 18, 19, 20, 50, 69, 91) also may be of relevance.

Histamine definitely is not the only relevant mediator substance in the pathophysiology of atopic eczema; it may, however, serve as a marker of mast cell and basophil activation. Similar results of increased formation of leukotriene B_4 in involved skin of patients with atopic eczema (75) as well as enhanced in vitro leukotriene B_4 secretion from peripheral leukocytes in atopic patients have been reported (76).

Psychosomatic interactions, histamine and atopic eczema

The in vivo and in vitro demonstrable dysregulation of the autonomic nervous system in patients with atopic eczema (33, 43, 44, 56, 68, 94) together with the role of autonomic nervous system transmitters in regulating histamine release (inhibition by β-adrenergic, enhancement by cholinergic stimuli) (27, 46, 64, 65, 78, 86) and the possible existence of a newly described H3-receptor in the brain might open a new field of research in order to more clearly define the nature of psychosomatic interactions in this disease (10, 67, 92). This new H3-receptor has been demonstrated in the rat brain where it serves as an autocrine feed-back inhibitor of histaminergic neurones leading

Table III. *Histamine and atopic eczema*

In vivo
Histamine concentration elevated in the skin (±)
Histamine elevated in plasma (during exacerbation)
In vitro
Altered releasability
Increased release from basophil leukocytes
Increased speed of release
Influence of autonomic nervous system transmitters
Modulation by arachidonic acid metabolites

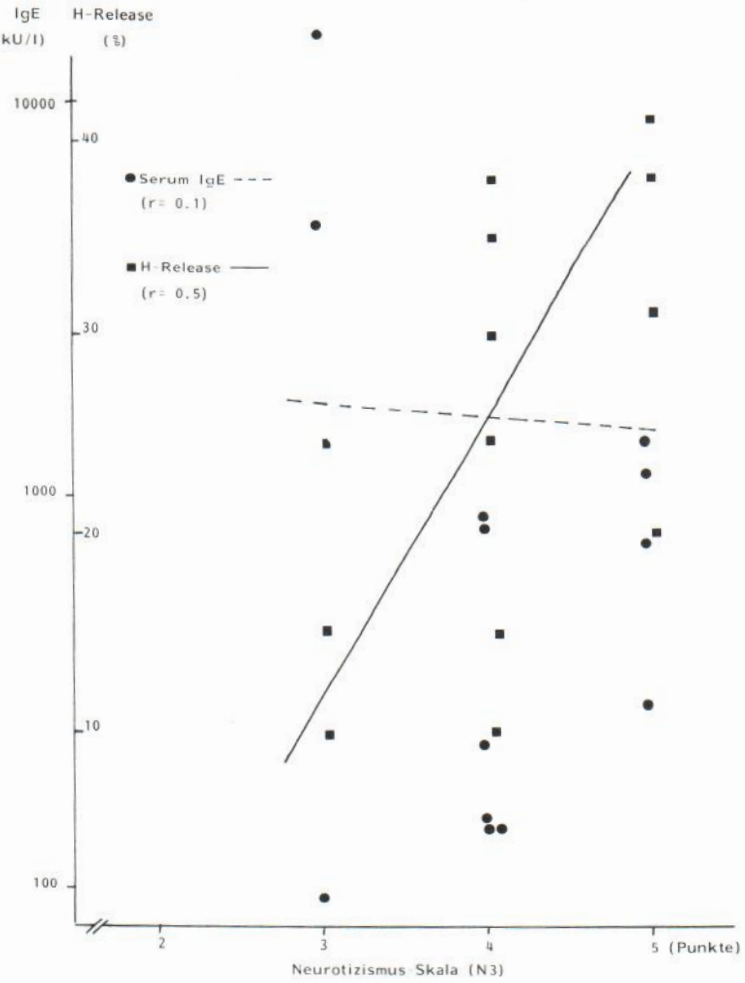

Fig. 3. Correlation of psychodiagnostic test results in the neuroticism scale of the "Hamburg Neuroticism and Extraversion Scale" (HANES) for children and adolescents to somatic findings as serum IgE concentration and in vitro histamine releasability after anti-IgE-stimulation of peripheral leukocytes.

to diminished histamine synthesis in and synaptic secretion from these cells (4, 81 *a*).

It has been shown by various authors that histamine release can be induced by stress in various forms (60, 69).

In a psychosomatic investigation using several psychodiagnostic tests in children with atopic eczema and control children with non-inflammatory dermatologic diseases we compared the results of the "Hamburg Neuroticism and Extraversion Scale" (HANES) for children and adolescents with somatic findings as extent of skin lesions, serum IgE-level and in vitro histamine releasability (67). As shown in Fig. 3 there was no correlation between the results of the psychodiagnostic tests to any somatic finding except for the slightly pronounced positive correlation between in vitro histamine releasability towards anti-IgE and neuroticism as measured in the HANES scale (Fig. 3).

Therapeutic approaches

Therapeutic approaches to histamine-mediated diseases can act at different stages (Table IV) from the inhibition of histamine synthesis via blockade of histamine release at different levels until specific antagonism of histamine effects (Table IV) (11, 24, 58, 68, 94).

In antihistamine therapy new developments include the production of non-sedating H1-antagonists, the combination of H1- and H2-antagonists as well as the application of H1-antagonists with mast cell blocking activity (Table V).

The side effects of classical H1-antagonists include mostly sedative effects; it seems of interest, however, that in double-blind studies these sedating side effects are observed regularly, especially in a certain percentage of atopic patients even under placebo (Table VI).

There is some controversy regarding the effect of

Table IV. *Therapeutic modalities in histamine-mediated diseases*

Histamine synthesis inhibitors
Histamine release blockers
cAMP-active substances
Flavonoids
Ca-antagonists (?)
Inosiplex (?)
Lipoxygenase inhibitors
Histamine antagonists

Table V. *Antihistamine therapy*

H1-antagonists (classic)
H1-antagonists (non-sedating)
H1-antagonists with mast cell blocking activity
H2-antagonists
H1- + H2-antagonists combined
H3-agonists or antagonists (?)

Table VI. *"Antihistamine"-side effects under placebo treatment (%)*

Sedation	13
Headache	6
Dryness of mouth	5
Diarrhoea	2
Nausea	2
Abdominal pain	2
CNS-stimulation	1
Exanthema	1
Increase in body weight	1

Table VII. *Antihistamines, itch and atopic eczema*

H1/H2 antagonists not superior to H1 or H2 alone (Foulds & Mackie, 1981)
Terfenadine, astemizol (1 dose) no effect upon endogenous, but upon peripherally induced itch (Krause & Shuster, 1983)
H1/H2 not superior to H1 but positive trend regarding itch (Frosch et al., 1984)
Histamine antagonism independent of sedation (Hägermark et al. 1985)
Tazyfylline no effect upon itch and scratch response in atopic eczema (Savin et al., 1986)
Tazyfylline dose-dependent effect upon peripherally induced itch (Ring et al., 1988)
Oxatomide effective in atopic eczema (placebo control) (Weinberg & Leaver, 1987)
Terfenadine, Ketotifen both effective equally (Tholen et al., 1987)
Subjective feeling of sedation independent of objective parameters (driving performance) (Ring & Bieber, 1987)
Dimetinden, astemizol equally effective (Kiehn & Rakoski, 1987)

antihistamine therapy in atopic eczema. Especially with regard to the question whether sedating side-effects are essential for a possible therapeutic effect of antihistamines. In Table VII some studies from the literature are enlisted dealing with the efficacy of antihistamines upon itch or atopic eczema.

Obviously more studies will have to be done to really answer these questions. So far it seems to be fair to state that antihistamines can never represent the one and only therapeutic modality in this disease; on the other hand antihistamines have their place among many other therapeutic approaches in the treatment regimen of atopic eczema (11, 56, 68, 94).

New approaches include the application of mast cell blockers like oral cromoglycate, where we found some beneficial effect in an open clinical trial especially in patients with evidence for food allergy (45).

The modulation of fatty acid metabolism, either by giving gamma-linoleic acid (77, 93) or eicosapentainoic acid (EPA) is under investigation. Our results with a double-blind controlled study with EPA in atopic eczema showed no effect compared to placebo (to be published).

Future studies in the field of mediator research may lead to new therapeutic approaches for the treatment of atopic eczema.

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