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Leukotrienes in Atopic Eczema

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Involved skin in atopic eczema contains elevated levels of the 5-lipoxygenase metabolite of arachidonic acid, leukotriene B_4. In addition, leukocytes of atopic eczema patients produce increased amounts of eicosanoids upon immunological challenge. These facts and the biological effects of eicosanoids suggest their involvement in the pathogenesis of cutaneous inflammation in atopic eczema, and may provide a new target for pharmacological treatment of this disease.

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Inflammatory mediators are assumed to play an important role in the pathophysiology of cutaneous inflammation in atopic eczema. In skin, these molecules are formed predominantly by macrophages and granulocytes; other cell types, however, particularly keratinocytes, also possess the capacity to form inflammatory mediators and cytokines. The biological activities of mediators speak in favour of their involvement in atopic eczema. They cause:

erythema and oedema by influencing the function of cutaneous microvasculature;

inflammatory infiltrate by their chemotactic activity towards leukocytes;

hyperproliferation of epidermis by stimulating cell growth;

regulation of cellular immune phenomena.

Histamine, the classical mediator of inflammation, is present in biopsies from atopic eczema skin in normal concentrations (1). In a case of hyper-IgE-syndrome however, cutaneous histamine levels were maximally elevated. This finding may partly explain the propensity of patients with this disorder to develop skin infections. Despite normal steady state concentrations of histamine in skin, immunological challenge of biopsy pieces led to enhanced histamine release in atopic versus normal subjects. Still, histamine seems not to play a central role in the pathophysiology of atopic eczema, as can already be deduced from the lack of antieczematous properties of antihistamines despite their usefulness as antipruritic drugs.

Therefore, particular interest centers around eicosanoids, which exhibit all biological activities typical of inflammatory mediators. These substances are derivatives of arachidonic acid (eicosatetraenoic acid) which are formed via several enzymatic pathways. The enzyme cyclooxygenase forms the prostaglandins (PG) E_2, F_2 and D_2 as well as prostacyclin and thromboxane. 12-lipoxygenase synthesizes 12-HETE, and the 5-lipoxygenase enzyme forms 5-HETE and the leukotrienes (LT)B_4, C_4 and D_4. Glucocorticosteroids inhibit the formation of all eicosanoids by blocking the activity of the rate limiting enzyme phospholipase A_2, which releases arachidonic acid from cell membrane phospholipids. This action of the most important antiinflammatory drugs in dermatology points to the possible importance of eicosanoids in inflammatory skin diseases. A monograph reviewing the role of eicosanoids in the skin will give a detailed overview about this field (2).

We performed a systematic study analyzing the concentrations of eicosanoids in lesional and uninvolved skin of patients with atopic eczema in comparison with normal controls and patients with psoriasis (3). No elevation of PGE_2 could be measured in either dermatosis. PGD_2, the main product of arachidonic acid formed by mast cells, could not be detected in suction blister fluid in any of the patient groups using two radioimmunoassays. In contrast, in both diseases a selective elevation of the 5-lipoxygenase metabolite LTB_4 was found. This finding does not represent the simple consequence of cutaneous inflammation, because in UV-B-induced dermatitis, there are normal LTB_4 concentrations in the skin (4).

The elevated eicosanoid levels in tissues could be the result of an enhanced "releasability" of inflammatory mediators in atopic subjects. Leukocytes of patients with atopic eczema showed increased production of eicosanoids after immunological stimulation compared to cells from healthy controls (5).

Inflammatory mediators not only are able to explain the inflammatory changes in the skin, but also may account for the disturbed immune regulation in atopy, because histamine, PGE_2 and LTB_4 may cause a negative feedback regulation of the immune response (6).

Eicosanoids could represent potentially useful targets for pharmacological manipulations in atopic eczema. Inhibition of 5-lipoxygenase with or without cyclooxygenase may be one approach. Alternatively, the identification of LTB_4/12-HETE-receptors on epidermal cells (7) could give rise to the development of specific receptor antagonists.

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