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Abnormal Cutaneous Neurosensitivity in Atopic Skin

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Having found an inability of patients with atopic exczema to distinguish different levels of iontophoretically applied histamine concentrations, as shown by their diminished vascular reactions and itch responses, and reviewing this result in the light of our new findings of smaller flare reactions and weaker itch sensations following different concentrations of intradermally injected substance P, we have concluded that unmyelinated afferent skin nerve fibres in these patients seem to be affected by the pathophysiological mechanism of atopic eczema. We therefore suspect that a down-regulation of histamine receptors at nerve endings compensates for elevated histamine release from cutaneous mast cells in patients with atopic eczema.

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The physiological mechanisms underlying the initiation of pruritus are not yet fully understood. However, it is known that release of histamine from cutaneous mast cells is an important factor in inducing itch sensation. Histamine affects capillary permeability, resulting in wheals, and excites chemosensitive unmyelinated afferent nerve fibres, resulting in impulses to the central nervous system and peripheral release of neuropeptides such as Substance P. This reaction contributes to extended flare responses in these patients. Substance P acts as a strong histamine releaser, inducing cascade-like histamine reactions.

The slowly spreading erythema which appears after noxious skin irritation can be explained as follows: the noxious stimulus generates an afferent impulse which travels upwards, orthodromically, to the point of remification of the terminal branches of the neuron, then descends into another branch in antidromical direction leading to release of vasoactive substances from these nerve ending.

This stimulus therefore initiates an orthodromic impulse, resulting in a sensation of pain or itch, whereas another impulse travels antidromically to the peripheral nerve endings with the release of neuropeptides, such as substance P. Substance P effects degranulation of cutaneous mast cells and the resulting release of histamine, which itself excites other nerve fibres and produces plasma extravasation (wheal) and vasodilation (flare). This reaction can be observed over a discrete distance and is therefore called the 'cascade model' of Lembeck (1).

Antidromically induced vasodilation is also called 'neurogenic inflammation' (2). This complex reaction reflects a nocifensive reflex mechanism of the skin.

The receptive endings of small unmyelinated nerve fibres (= C-fibres) responsible for itching, which are excited by the mechanisms described above, are localized between corium and epidermis. Deeper application of these stimuli will not elicit itch, but rather pain. After blocking different nerve fibres it has been demonstrated that experimentally induced itching persisted when all myelinated fibres were blocked (3). Therefore unmyelinated C-fibres are responsible for the sensitivity of itch. Microneurographic experiments have shown that itch is transduced by a subpopulation of polymodal C-fibre nociceptors (4).

Considering the prominent role of histamine in the initiation of itch and the role of pruritus in atopic eczema, it is surprising that several researchers have found diminished wheal and flare reactions in atopic eczema patients after intradermal application of histamine (5, 6). However, the itch reactions of these patients were generally not assessed in these studies and often only one histamine dose was applied.

Therefore, we investigated the itch sensitivity and skin reactivity in 27 patients suffering from atopic eczema and 20 healthy controls after iontophoretically applied histamine at five different charges (7). Atopic eczema patients reacted with smaller wheal and flare sizes, compared with the controls. The itch rating results indicate that the patient group, in contrast to the controls, were unable to distinguish between weak and strong histamine stimuli. The patients rating to the strongest histamine stimulus were significantly lower than those of the controls.

These results indicate that atopic eczema patients' cutaneous nerve fibres are among the tissues hyposensitized to histamine, as they show a reduced ability to signal different levels of itch to the central nervous system and seem to react with a diminished release of vasoactive neuropeptides from afferent nerve fibres upon stimulation with histamine. The latter is indicated by decreased flare responses because the extent of flare response has previously been shown to depend on the afferent innervation.

In a follow-up study we investigated the cutaneous vasoreactivity and itch or burning pain sensitivity in 20 patients with atopic eczema and 20 healthy controls after intradermal injection of substance P (four different concentrations) and topical application of mustard oil (three different concentrations). This study has been published recently (8). Substance P evokes release of histamine from cutaneous mast cells by an indirect effect and induces plasma extravasation by a direct effect on the small skin blood vessels, seen as wheal eruption. Mustard oil excites unmyelinated polymodal nerve fibres and evokes neurogenic inflammation with burning pain. Mustard oil was used to obtain additional information about substance P release from afferent nerve endings.

Substance P evoked dose-dependent wheal-and-flare reactions in both groups. However, the patient group showed

significantly weaker reactions of three substance P concentrations. The neurogenic inflammation after mustard oil application was similar in both groups, and also dose dependent. Substance P induced itching starter significantly later in the patient group and was reported to be significantly weaker at one substance P concentration. Patients reported burning pain significantly later at two Mustard oil concentrations, the intensity of burning pain, however was the same in both groups.

After having found a smaller blood flow increase and a diminished ability to distinguish weak from strong histamine stimuli after ionthphoretically applied histamine in atopic eczema patients, compared with controls, the findings after substance P injection confirm the hypotheses that the spontaneous and intense itch of atopic eczema patients leads to a hyposensitization to histamine of the fine peptidergic afferent nerve fibres.

The down-regulation of the histamine receptors probably compensates for the higher histamine concentrations in the skin of atopic eczema patients which were observed by earlier investigators (9), whereas later studies reported normal histamine concentrations in those patient's skin (10). This does not exclude an increased release of histamine by cutaneous mast cells in atopic eczema patients. A very short histamine halfline in the skin prior to reabsorption could result in the normal concentrations found in cutaneous histamine measurements.

As a result of our findings, we suspect a diminished axon reflex in these patients as it relates to histamine. This might lead to a disturbed nocifensive reflex function of the skin in atopic eczema patients.

However, it is still not clear whether these findings are a result of chronically inflamed skin in these patients, or are an independent phenomenon.

How can we explain the paradoxically strong and intense itch and the diminished reactivity to histamine in these patients? Disturbances in the central nervous system regulating itch sensation might account for this effect. Furthermore, it is still not known if other transmitters are responsible for the intense and severe itch associated with atopic eczema. These observations provide an explanation of why peripheral acting antihistamines have only a weak antipruritogenic effect on the itch symptoms of atopic eczema patients.

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