

# Itch in Atopic Dermatitis – Pathophysiology and Treatment

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Received: July 7, 2010

Accepted: October 12, 2010

**SUMMARY** Pruritus is an essential feature of atopic dermatitis with a high impact on the quality of life. Although the pathophysiology of atopic dermatitis itch is not fully understood, recent studies have demonstrated that a variety of mechanisms contribute to the induction and maintenance of the symptom. For example, an increased number of cutaneous nerve fibers and neuropeptides were identified in atopic dermatitis skin. Histamine and histamine 4 receptor as well as interleukin 31 are novel key players identified in itch induction, in addition to inflammatory cells such as mast cells, eosinophils and lymphocytes. The new findings suggest that target-specific therapies are most likely to control atopic dermatitis itch. To date, only few therapies are available and controlled studies are pending.

**KEY WORDS:** atopic dermatitis, pruritus, histamine 4 receptor, interleukin 31, sensory nerves

## INTRODUCTION

Pruritus is an essential feature of atopic dermatitis (AD) (1), with a high impact on the quality of life. Many patients measure the severity of the disease by the intensity of pruritus rather than by the appearance of skin lesions. Although pruritus is a main symptom of AD, its pathophysiology is still not fully understood. As a cutaneous sensory perception, itch is excited on neuropeptide-containing unmyelinated nerve fibers in the papillary dermis and epidermis. Several mediators such as neuropeptides, interleukins, proteases or cytokines are known to provoke itch in AD by direct binding to itch receptors or indirectly *via* histamine release. Recent studies have revealed novel aspects of the pathophysiology of itch in AD and suggest new treatment possibilities.

## NERVOUS SYSTEM IN ATOPIC DERMATITIS

Several investigators have demonstrated that there are alterations in the number of cutaneous nerve fibers in AD skin lesions. An increase of sensory but decrease of adrenergic autonomic nerve fibers was observed (2), indicating a differential role of primary afferent and autonomic nerve fibers in pruritus pathophysiology. Immunohistochemical analysis of neuropeptide distribution in cutaneous nerve fibers showed in lesional AD skin increased numbers of neurofilament-, protein gene product (PGP) 9.5-, calcitonin gene related peptide (CGRP)-, and substance P (SP)- positive nerve fibers in the papillary dermis (3), at the

dermoepidermal junction (4), in the epidermis (2) and around sweat glands. In a semiquantitative analysis, Sugiura *et al.* (3) found different densities of PGP 9.5-positive peripheral nerves in early acute lesions of AD ( $2.5 \times 10^3 \mu\text{m}^2/\Delta\text{s}$ ), subacute lesions ( $3.8 \times 10^3 \mu\text{m}^2/\Delta\text{s}$ ), lichenified lesions ( $4.9 \times 10^3 \mu\text{m}^2/\Delta\text{s}$ ) and prurigo lesions ( $7.1 \times 10^3 \mu\text{m}^2/\Delta\text{s}$ ), in comparison to the skin of patients with AD without such lesions ( $2.0 \times 10^3 \mu\text{m}^2/\Delta\text{s}$ ). Hypertrophy of nerve fibers in AD is possibly stimulated by an increased release of nerve growth factor secreted by basal keratinocytes (5). Interestingly, a recent animal model showed an increased number of gastrin releasing peptide (GRP)- and SP-positive nerves (6). GRP is specifically expressed in itch-sensitive fibers (7) in contrast to PGP 9.5, which stains all nerves including those sensitive for pain and touch. In sum, in AD skin, itch fibers and their neuropeptides are increased.

## ITCH INDUCTION: MEDIATORS AND MECHANISMS

Itching reflects a distinct quality of cutaneous nociception elicited by chemical mediators and other stimuli to neuronal receptors. Several studies could demonstrate that itch in individuals with AD follows different pathways as compared to non-atopic individuals. For example, while normal volunteers experience intense pruritus after injection of histamine or substance P, patients with AD notice only weak itch sensations. On the other hand, application of acetylcholine results in pruritus rather than pain in AD patients.

### Histamine 1 and 4 receptor

Many mediators triggering itch have been investigated in AD. Among them, histamine has been a persistent candidate and is the most thoroughly studied pruritogen for decades. Histamine binds to histamine 1 (H1) receptor expressed on sensory nerve fibers and endothelial vessel walls. Intradermal injections of histamine provoke vasodilation with redness, wheal and flare (the so-called triple response of neurogenic inflammation) accompanied with pruritus. Williams (8) suggests that histamine may play a role in the pathogenesis of AD since intramuscular histamine injections resulted in pruritus. Elevated histamine levels in both lesional and uninvolved skin in AD patients were also reported (9). Several authors noticed reduced itch sensations in response to either intracutaneously injected or iontophoretically applied histamine when compared to non-atopic

healthy subjects (10). Furthermore, intradermally injected SP releases histamine and provokes diminished itch perception in patients with AD in comparison to healthy subjects, which underlines the minor capacity of histamine to induce pruritus in AD (11). These conflicting results of elevated levels of histamine and diminished itching after histamine application may indicate either an intrinsic down-regulation of neuronal H1-receptor density or affinity, or increased histamine degradation in atopic skin. Consequently, antihistamines in normal dosages are of weak efficacy in AD, as demonstrated in experimental studies as well as in double-blind, cross-over trials (12). For example, Wahlgren *et al.* (13) compared the antipruritic effect of H1 antagonist and placebo in AD patients and found no difference between these two agents.

Recently, histamine 4 (H4) receptors were found on inflammatory cells, mainly mast cells, eosinophilic granulocytes and T-lymphocytes (14). Gutzmer *et al.* showed that the Th2 lymphocytes of AD patients expressed a functionally active H4 receptor (15). Stimulation of H4 receptor leads to up-regulation of the pruritogenic interleukin IL31. This newly found mechanism may explain the quick increase in pruritus intensity during flaring up of AD patients. Interestingly, a mouse model suggests that a combination of H4 and H1 receptor antagonism might be a new strategy to treat pruritus related to allergic diseases like AD. In their experiments, the authors showed that H4 receptor antagonism failed to reduce the allergic inflammatory response but strongly inhibited allergen-induced itch (16). In sum, these results support the idea that histamine and the histamine 4 receptor but to a lesser degree also histamine 1 receptor are involved in AD pathophysiology.

### Neuropeptides

Several observations support the idea of an important role of neuropeptides in the pathophysiology of pruritus in various skin diseases (5). Neuropeptides such as SP, VIP, somatostatin, and neurotensin provoke itch along with the characteristics of neurogenic inflammation such as erythema, wheal and flare. SP induces itch responses in humans and mice, which are mediated *via* activation of the neurokinin 1 receptor (NK1R) on mast cells and keratinocytes, resulting in enhancement of inflammatory responses (17), thus supporting an indirect effect of SP in mediating pruritus. In patients with AD, alterations in the nerve fiber containing neuropeptide profile could be demonstrat-

ed. Somatostatin-immunoreactive nerve fibers were decreased in AD patients (18). NPY-positive nerve fibers and Langerhans cells were increased as compared to healthy controls (18). Moreover, tissue concentrations of VIP were decreased while SP concentrations were increased in lesional skin of AD patients (19). In contrast, the staining pattern for CGRP was not altered in comparison to controls (18). These observations support the idea that an imbalance of the cutaneous nervous system including nerve fibers, neuropeptides and their receptors as well as neuropeptide-degrading enzymes may play a crucial role in the pathophysiology of pruritus in AD. Targeting the neuropeptides is a new concept in the treatment of AD itch. For example, a case series applying the NRK1 antagonist aprepitant showed significant antipruritic effects in patients with atopic predisposition (20). Controlled trials are pending.

### **CYTOKINES AND INFLAMMATORY CELLS INVOLVED IN THE PATHOGENESIS OF PRURITUS IN ATOPIC DERMATITIS**

Cytokines are released from various cutaneous and immune cells during inflammation. Certain cytokines have been demonstrated to induce pruritus and activate neuropeptide release from sensory nerves in the skin of AD patients.

#### **Interleukin 2**

While IL-1 does not seem to correlate with itching, interleukin 2 (IL-2) is claimed to be a potent inducer of pruritus. As observed upon therapeutic application, high doses of recombinant IL-2, as given in cancer patients, frequently provoked redness and cutaneous itching (21). Furthermore, AD patients treated with oral cyclosporin A, a drug that inhibits the production of various cytokines including IL-2, experienced attenuation of itch. Additionally, a single intracutaneous injection of IL-2 induced a low-intensity intermittent local itch with maximal intensity between 6 h and 48 h as well as erythema in both atopic and healthy individuals (22). Interestingly, in AD patients, this reaction appeared earlier than in healthy controls. Moreover, bradykinin appears to enhance the effect of IL-2-induced pruritus on sensory nerves (23). Upon prick testing, supernatants of mitogen-stimulated leukocytes were pruritic in AD patients but not in controls, probably due to the increased concentration of IL-2 and IL-6 (24). The mechanism for the induction of itch by IL-2 remains to be established,

but the latency preceding the itch response after injection in AD patients suggests an indirect pruritogenic effect of IL-2 *via* other mediators.

#### **Interleukin 6**

Interleukin 6 (IL-6) and IL-6 receptor are expressed in nerve and Schwann cells and IL-6 like immunoreactivity was increased in nerve fibers of patients with positive epicutaneous patch tests and prurigo nodularis (25), suggesting a role for this cytokine in pruritus. Several studies suggest that IL-6 does not play a major role in pruritus in AD (25). In a clinical trial with AD patients, decreased sleep efficiency was associated with increasing disease severity, scratching, and IL-6 levels, suggesting an important relationship between sleep and IL-6 (26).

#### **Interleukin 8**

Recently, various studies revealed increased levels of the proinflammatory chemokine IL-8 in lesional skin, plasma, and blood mononuclear cells, especially eosinophils of AD patients (27). However, the capacity of IL-8 to induce pruritus is questionable since prick testing with IL-8 does not induce whealing or pruritus. Further studies will have to clarify the influence of IL-8 in the pathophysiology of pruritus.

#### **Interleukin 31**

The newly discovered interleukin, IL-31, might have a major role in the pathophysiology of AD pruritus (28). For example, IL-31 mRNA in the skin of NC/Nga mice with scratching behavior was found to be significantly higher than that in NC/Nga mice without scratching behavior (28). Moreover, IL-31 was significantly overexpressed in human AD skin compared with nonpruritic psoriatic skin inflammation (29). The authors could also demonstrate a link between bacterial colonization and induction of pruritus. Staphylococcal superantigen rapidly induced IL-31 expression in atopic individuals. *In vitro*, staphylococcal enterotoxin B but not viruses or T(H)1 and T(H)2 cytokines induced IL-31 in leukocytes. In patients with AD, activated leukocytes expressed significantly higher IL-31 levels compared with control subjects. IL-31 receptor A showed most abundant expression in dorsal root ganglia representing the site where the cell bodies of cutaneous sensory neurons reside. These results suggest a direct link among staphylococcal colonization, subsequent T-cell recruitment/activation, and pruritus induction in patients with AD (29).

### Neurotrophin-4

Recent observations indicate that neurotrophin-4 (NT-4) may be involved in inflammatory and itch responses of patients with AD. NT-4 is a keratinocyte-derived factor which is highly expressed under inflammatory conditions and which exerts growth-promoting effects on nerve cells. Accordingly, NT-4 expression was found to be significantly increased in lesional skin of patients with AD and in prurigo lesions of AD skin (30). A recent study suggests that prostaglandin E2 (PGE2) enhances NT-4 production *via* EP3 receptor (31). It has been suggested that PGE2 may promote innervation in skin lesions with AD *via* NT-4 induction. NT-4 production can also be induced by INF- $\gamma$ , which itself is known to have a beneficial effect on pruritus. These findings suggest a close relationship between immune and neurotrophic factors in the pathophysiology of pruritus in AD.

### Nerve growth factor

Nerve growth factor (NGF) is released by keratinocytes, mast cells and eosinophilic granulocytes, and increased levels of NGF are found in AD skin (32). NGF is believed to sensitize peripheral nerve endings facilitating induction of pruritus. Sprouting of epidermal nerve fibers as found in lesional AD skin is attributed to increased NGF expression in AD (4). In addition, remarkably increased serum levels of NGF and substance P were found to correlate with the severity of the disease in AD (32,33). Increased epidermal NGF expression was observed in an animal model of AD (NC/Nga mice). Moreover, therapeutic anti-NGF approaches reduced pruritus successfully, thus representing a promising future therapeutic option for pruritus in AD (34).

### Eosinophils

The role of eosinophils in the pathogenesis of AD has not yet been fully understood; however, it seems likely that they contribute to the induction and maintenance of pruritus. Eosinophils may have direct contact with nerve fibers and release factors which may have a direct pruritogenic effect, such as eosinophil-derived neurotoxin (EDN), NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), platelet-activating factor (PAF), leukotrienes, prostanoids, kinins, cytokines, and proteases (35). They may also elicit an indirect itch response by activating mast cells to release histamine or proteinases. In summary, it may be speculated that eosinophils and their me-

diators contribute to direct induction of pruritus as well as to sensitization and nerve fiber sprouting in AD.

### THERAPY

Some general principles should be borne in mind in the management of pruritus of any origin including AD (Table 1). First, provocative and exacerbating factors like wool fibers must be eliminated. Furthermore, since scratching also represents a trigger factor and maintains the itch-scratch cycle, it must be interrupted by education of the patient to control scratch behavior. For example, the behavior method 'habit reversal' can be employed (36). To reduce sweating-induced itch, simple skin care such as taking a warm shower and application of ointment is recommended. Cooling the skin with lotions containing, e.g., menthol results in relief of itch (37). To combat skin dryness, application of hydrophilic emollients and bathing with oily bath additives is helpful. Topical anesthetics are reported to be useful in pruritus, albeit no effect was observed in AD patients (38). Unspecific physical modalities are described to be beneficial, e.g., acupuncture (39) and cutaneous field stimulation (40).

### Specific antipruritic therapies

Although various symptomatic treatments are employed to relieve pruritus and scratching in patients with AD, no specific therapies are available as of yet. Since lesional AD skin shows a dense inflammatory cell infiltrate known to mediate or aggravate pruritus, anti-inflammatory therapies often result in cessation of pruritus. Systemic and topical immunomodulators such as glucocorticoids, cyclosporin A, tacrolimus, pimecrolimus and ultraviolet light therapy continue to be consistently the most effective antipruritic agents (41-44). Moreover, there are no evident and efficient alternatives to topical application of corticosteroids for the control of acute episodes in AD (45). The reduction of skin lesions results in a decreased itch intensity, probably due to the reduction of inflammatory cells and protection of depolarization of nerve fibers mediated directly by the steroid (46). Cyclosporin A (CyA) has been reported to have an itch-relieving effect in various diseases including AD. In a randomized study, CyA was demonstrated to significantly reduce itch intensity (41). On discontinuation of this therapy, pruritus recurred immediately, suggesting that CyA represents a symptomatic and not causal therapy of pruritus. A case series reported relief of itch and scratch lesions in prurigo forms of AD

**Table 1.** Therapeutic strategies combating pruritus in atopic dermatitis

Therapeutic modality	Examples
General principles	Elimination of provocative factors Skin care to reduce sweating-induced itch Therapy of eczema and scratch lesions
Unspecific topical preparations	Emollients Lotions containing cooling additives, menthol Bathing with oily additives
Unspecific physical modalities	Physical exercise* Acupuncture Cutaneous field stimulation
Anti-inflammatory therapy	Corticosteroids, t and o* Cyclosporin A, o* Tacrolimus, t* Pimecrolimus, t* Palmitoylethanolamine (PEA), t Ultraviolet light
Target-specific therapies	Capsaicin, t Doxepin (but: contact allergy upon long-term application), t PUVA Aprepitant, o
Contradictory results	H1-Antihistamines, o

\*as proven by randomized, controlled studies; t = topical; o = oral; i.c. = intracutaneous; i.v. = intravenous

(47). The topical immunomodulators tacrolimus and pimecrolimus were frequently demonstrated to reduce erythema as well as pruritus and excoriations. Randomized studies confirmed topical administration of both to be antipruritic in adults and children (2-15 years) with AD (42,44). Since both have inhibitory effects on the production of pro-inflammatory cytokines by T-cells and mast cells, the specific improvement of pruritus suggests interference of calcineurin inhibitors with the neuro-immune network in the skin of patients with AD. In addition, it is speculated that they bind to the capsaicin receptor TRPV1 to mediate initial burning (neurogenic inflammation), followed by rapid reduction of pruritus (48,49).

Systemic administration of endogenous and synthetic cannabinoids is known to have psychotropic and analgesic potency. Recently, both cannabinoid receptors CB1 and CB2 were found to be expressed on cutaneous sensory nerve fibers, mast cells and keratinocytes (50). It was demonstrated that injections of the CB2 agonist N-palmitoylethanolamin (PEA) inhibited NGF-induced thermal hyperalgesia (51). In a large collective of AD patients (2456 patients aged 2 to 70 years), a pilot trial using a PEA-containing cream resulted in relief of pruritus (52). These preliminary data suggest that topically applied cannabinoid agonists may have a role in future models of antipruritic therapy.

Since several studies have demonstrated that different nociceptive mechanisms are involved in AD, it is not surprising that conventional therapeutic modalities like antihistamines often fail to ameliorate pruritus in AD (12). This is in agreement with the idea that histamine is not the major mediator of pruritus in AD (10). Placebo-controlled studies concerning the antipruritic effect of oral antihistamines have shown conflicting results in AD. In some studies, antihistamines demonstrated no superior effect compared to placebo, whereas in others, they showed a significant antipruritic effect (12,13,53). The H1-antihistamine cetirizine has been reported to focally reduce itch. However, an evidence-based review of the efficacy of antihistamines in relieving pruritus in AD has concluded that little objective evidence exists for the antipruritic efficacy of H1-antihistamines in AD (12). It has been suggested that topical application of the tricyclic antidepressant doxepin might have antipruritic effects because of its high affinity to H1 histamine receptors. The use of 5% doxepin cream resulted in improvement of histamine-induced and SP-mediated cutaneous responses, but also led to sedative effects in some patients (54). Unfortunately, doxepin was accompanied by contact allergies after long-term application (55).

There are several therapies that target specific aspects of the pathophysiology of pruritus.

For example, PUVA has been described to reduce neuronal hyperplasia and increased levels of NGF in AD patients (56). Neuropeptides are targeted by topical capsaicin, tacrolimus or systemic application of aprepitant (20,57) and appear to be promising new approaches in management therapy of AD. However, there are no controlled studies establishing a completely effective and safe antipruritic agent for the management of pruritus in AD. Further investigations are necessary to identify antipruritic substances that help interrupt the complex itch-scratch cycle by influencing the centrally and peripherally altered itch perception involved in AD.

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