REVIEW ARTICLE

Pathophysiology and therapy of pruritus in allergic and atopic diseases

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Abstract

Pruritus (itch) is a major characteristic and one of the most debiliating symptoms in allergic and atopic diseases and *the* diagnostic hallmark of atopic dermatitis. Pruritus is regularly defined as an unpleasant sensation provoking the desire to scratch. Although we achieved rather good knowledge about certain inducers of itch such as neuropeptides, amines, μ-opioids, cytokines and proteases, for example, less is known about the pathophysiological specifities among the different diseases, and the therapeutic consequences which may derive thereoff. This review dissects the role of mediators, receptors and itch inhibitors on peripheral nerve endings, dorsal root ganglia, the spinal cord and the CNS leading to the amplification or – vice versa – suppression of pruritus. As the treatment of pruritus in allergic and atopic skin disease is still not satisfactory, knowing these pathways and mechanisms may lead to novel therapeutic approaches against this frequently encountered skin symptom.

Itch transmission by the nervous system

The skin constitutes a barrier between 'outside' environment and 'inner' body. Therefore, one of its main tasks is to protect the organism against harmful influences from the outside. To fullfil this task, the skin is armed with an effective communication and control system. In all layers of the skin, specialized sensory and efferent nerve branches appear to form an overall dense nerval network. One main 'outside-to-inside' interaction causes sensations of itch. Pruritus is regularly defined as an unpleasant sensation provoking the desire to scratch (1) and constitutes an essential feature of atopic dermatitis (AD) (2, 3).

Abbreviations
ACh, acetylcholine; AD, atopic dermatitis; CB, cannabinoid receptor; CGRP, calcitonin gene-related peptide; CyA, cyclosporin A; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; IL, interleukin; IFN, interferon; NGF, nerve growth factor; NKR, neurokinin receptor; NPY, neuropeptide Y; NT, neurotrophin; PAR, protease-activated receptor; PGP, protein gene product; SP, substance P; TRPV1, transient receptor potential vanilloid (capsaicin) receptor 1; VIP, vasoactive intestinal polypeptide.

Based on early psychophysical studies on itch (4), it was believed that itch is nothing but a low-intensity pain. Concepts from those times declared that itch is enciphered in specific patterns of action potentials running through 'pain fibres' or that itch emerges from combinations of other primary sensory signals. However, it is clear at this stage that pruritoception is a distinct entity just as nociception is a distinct entity (5–8). Therefore, the new concept of itch transmission is based on an important proposition: the existence of a central itch-specific neuronal pathway, in other words, it envisages the existence of a sensory system for pruritoception that is distinct from the sensory system for nociception (Fig. 1).

Pruritus can be triggered by localized, systemic, peripheral or central stimuli. To relay itch information to different cerebric areas is the specific function of a subpopulation of the dense nerval network in the skin, the unmyelienated C-polymodal nociceptive neurons (in general being histamine-sensitive). The free nerve endings referred to as cutaneous terminals reside in the epidermis, papillary dermis and around skin appendages and are qualified to apprehend endogenous or exogenous itch causing agents through an armada of relevant receptors. These receptors detect their corresponding 'itchy' ligands and send either an electrical signal to the central

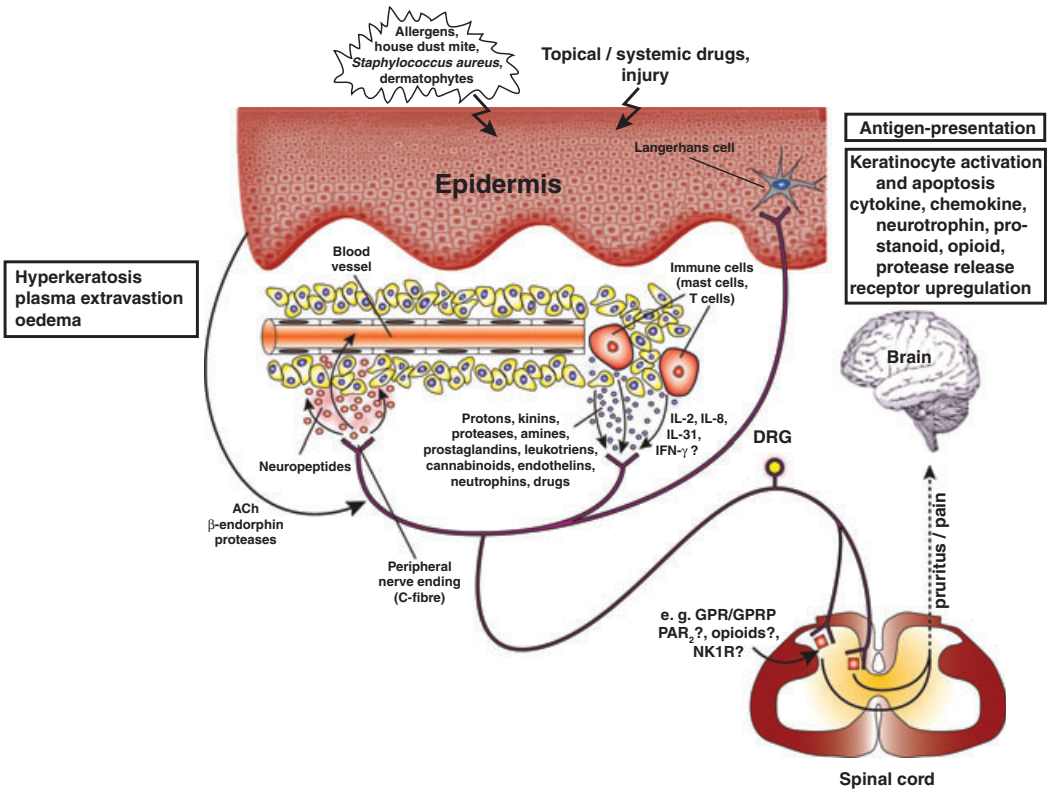

Figure 1 General neuroanatomical and neurophysiologcial pathways activated during pruritus (pruritogenic itch). Exogenous or endogenous meditors stimulate selective subtypes of peripheral C fibre nerve endings of primary afferent neurons in the epidermis or dermis. High-affinity receptors for various pruritogenic mediators transmit the stimulus, via not completely understood intracellular signaling pathways, from the periphery to the dorsal root ganglia (DRG), and the spinal cord. DRGs can modulate this stimulus on the transcriptional and posttranscriptional level, thereby modulating peripheral and central nerve endings. Within the spinal cord, itch signals can be also modulated. From lamina 1, a selective area within the the dorsal horn of spinal cord, the signal will be transmitted to the CNS after crossing to the contralateral side. Activation of specific areas in the CNS results in the perception of itch leading to 'discomfort' and an acute or chronic scratch response. Additionally, the associated peripheral axon reflex may lead to the release of mast cell-stimulating neuropeptides (e.g. substance P) thereby amplifying pruritus via release of histamine, tryptase and IL-31, for example. This figure does not consider the complex interaction between pain and itch fibres on the spinal cord level where GRPR, opioid receptors, NK1R (post-synaptic), PAR2 (pre-synaptic primary afferents) and probably other mediators/ receptors can exert exciatatory or inhibitory influences.

nervous system or trigger a direct inflammatory response by antidromic impulse transmission. From the foregoing, it is apparent that the nature of the ligand present and the corresponding accessory receptor determine the nerval reaction (7).

Sensory cutaneous nerves transmit the pruritic information to dorsal root ganglions and from there it reaches the spinal cord where it can be modulated. From the lamina I, a specific side within the dorsal horn of the spinal cord, the signal is projected to the thalamus (6, 9). On this passage, the signal crosses to the contralateral side. Nerval structures pertinent to the transmission of pruritic information in the spine are not clarified to date, but a subset of histamine- and GRP-sensitive neurons probably executes this assignment (5, 7, 10). A neurotoxic destruction approach carried out in rodents supplies evidence for a key role of NK-1 receptor expressing neurons in the transmission of itch information in the superficial spinal dorsal horn (11). Notably, ablation of NK1R-positive neurons compromises chronic pain behaviours in rat (12, 13), although the confirmation for a direct role of the NK-1 receptor in human spinal itch transmission is still lacking. From the thalamus, direct excitatory connections that consist of the anterior cingulate cortex, the insular cortex (insula) and primary and secondary somatosensory cortices take over (6, 9, 14–16).

Itch-specific mediators in the central nervous system are elusive and so far not known. However, recent evidence emerged that gastrin-releasing peptide receptor (GRPR), a bombesin-like peptide receptor homologue that is specifically expressed in the lamina I of the dorsal horn, might play a crucial role in mediating itch sensations in the spinal cord and might furthermore constitute a marker for central itch-selective neurons (10). Strikingly, selective ablation of lamina I neurons expressing GRPR in the spinal cord of mice resulted in severe deficiencies in scratching responses to an amarda of pruritogenic stimuli such as histamine, compound 48/80, serotonin, endothelin-1, PAR_2-activating peptide and the anti-malaria drug chloroquine (17). The severity of this

observation is that GPRP transmits itch signals independent of the nature of the pruritogenic stimulus. In fact, GRPR constitutes the long-sought labelled line for itch sensation in the spinal cord.

Cutaneous neuroreceptors and mediators: induction of pruritus

The induction of itch is accomplished by a variety of agents that ineract with a multitude of receptors on free nerve endings. Over the last decade of itch research, the number of pruritogenic agents has grown far beyond the usual suspect histamine. But it is the lot of several newly reported pruritic agents to lack appropriate recognition by the scientific community, while the potency of histamine to induce itch continues to be overestimated. In the following, the main mediators of cutaneous pruritus will be introduced and briefly described (see also Table 1).

Histamine

About 80 years ago, Lewis reported that intracutaneous injection of histamine causes symptoms characteristic of neurogenic inflammation – redness, wheal and flare – along with pruritus (18, 19). Furthermore, Williams (20) suggested that histamine may play a role in the pathogenesis of AD because intramuscular histamine injections resulted in pruritus. Based on these initial experiments, histamine has doubtlessly become the most exhaustingly investigated 'itchy' agonist. Over the years, elevated histamine levels in lesional and nonlesion al skin were detected (21, 22), topographically associating histamine and itch. The distinct source of skin histamine was attributed to mast cells and keratinocytes (23–25). Also to date, four distinct histamine receptors (H1-4R) have been identified that histamine is capable of activating (26). At least two of them, H1R and H2R, are present on cutaneous sensory nerve fibres (23, 27). Therewith, all ingredients have been provided to support histamine in being an important pruritogen, especially as H1R- (and less so H2R) antagonists have been demonstrated to reduce itch in numerous clinical trials (7, 28–30). However, re-evaluating the histamine content of the skin, recent investigations could not verify increased histamine levels in all pruritic diseases indicating a selective role of various mediators among the different pruritic diseases (31). And while re-evaluating the potency of histamine to induce itch, it was shown in recent studies that small doses of histamine fail to produce itch but still are sufficient to produce oedema and erythema upon intracutaneous

Table 1 Mediators of itch in atopic dermatitis

Substrate	Provocation of itch	Mechanism
Spinal inductor of itch		
GRP	+	Binding to GRPR of the spinal cord
Cutaneous inductors of itch		
Histamine	(+)	Binding to histamine receptors on sensory nerve fibres
Neuropeptides (e.g. substance P)	+	Mast cell degranulation, increased concentration in lesional skin
Acetylcholine	+	Central sensitization?
Tryptase kallikreins, cathepsin S	+	Binding to PAR_2 on sensory nerve fibres
Cytokines: Interleukin 2	+	Possible release of various mediators
Interleukin 8	–	
Interleukin 31	+	
Neurotrophin-4	+	m.n.n.
Eosinophils	+/?	Release mediators like PAF, leucotriens; histamine, proteinase liberation
Platelet activating factor	+	Histamine liberator
Leukotriens	+	m.n.n. (LTB4?)
Cutaneous suppressors of itch		
Cannabinoids	Interruption of itch transmission	Binding to CB1 and CB2 on cutaneous sensory nerve fibres
Opioid peptides	Induction of itch-inhibiting neurons on spinal level; suppression in the skin?	Binding to opioid receptors
TRP channels (Vanilloids)	Suppression of itch transmission	TRPV1, TRPV3 involved in itch Direct or indirect effects on sensory nerves suppressing itch
Interferon gamma	Suppression of pruritus	m.n.n. (IFN-γ receptor on nerves?)
Calcineurin inhibitors	Interruption of itch transmission	Downregulation of pruritic cytokines by effecting T cells Binding to TRPV1 on cutaneous sensory nerve fibres Ameliorating neuropeptide release Decreasing effects of neuropeptides on mast cells?

–, no induction of itch; (+), induction of weak itch; +, clear induction of itch; m.n.n., mechanism not known.

injection (32–35). Although in urticaria, the itchy role of histamine is well established, yet in patients with AD, intracutaneous injection and also iontophoretical application of histamine did not provoke an increase but a reduction in itch sensation (36–39). Additionally, intradermal injection of substance P (SP) in AD patients, an agonist stimulating histamine release from mast cells, as well produced a reduction in itch perception, which not only emphasizes the marginal capacity of histamine to induce pruritus in AD (40) but also lets one speculate about the general capacity of histamine as a potent pruritogen in AD. The last cloned histamine receptors, H3R and H4R, however, might bring histamine back into focus to reclaim a relative importance as a pruritogen because both operate at least in mice as itch receptors (41, 42). Only recently, the role of histamine H4 receptor (H4R) was investigated in a T-helper type 2 (Th2)-cell-mediated mouse skin inflammation model that mimics several features of AD (43). In this mouse model, H4R antagonists (e.g. the small compound JNJ 7777120) were utilized and showed strong anti-inflammatory effects along with significant inhibition of pruritus sensation. Their roles in humans though have to be investigated in future research. But independent of prospective insights into histamines role in itch, it already became clear that a variety of mediators have to be involved in this process.

Neuropeptides

Several observations support that neuropeptides provoke itch in human skin upon intradermal injection. For example, SP, a neuropeptide causing the characteristic trias of symptoms of neurogenic inflammation (wheal, flare, oedema), further provoked itch after its intradermal injection. The itchy action of SP was inhibited by antihistamines and compound 48/80 which clearly demonstrated an involvement of mast cell degranulation and concomitant release of mast cell mediators in this process (42). Vasoactive intestinal peptide (VIP), somatostatin, secretin and neurotensin seem to utilize this same pathway (42, 44–47). The concept for the pathophysiology of itching caused by these neuropeptides is believed to rest upon their imbalanced cutaneous expression (48–50). This imbalance can be reflected by morphological alterations as in patients with allergic or AD alterations in the nerve fibre containing neuropeptide profile account for the imbalance. In this case, somatostatin-immunoreactive nerve fibres were decreased in AD patients, for example (51), whereas on the other hand, nerve fibres positive for neuropeptide Y (NPY) were increased (51–53). Accordingly, while the tissue concentrations of VIP were decreased, the SP concentration was increased in lesional skin (54–56). However, the SP-induced itch responses are eventually mediated in mice by direct neurokinin receptor 1 (NK1R) activation, pointing at a direct effect of SP in mediating pruritus *in vivo* (57–59). The NK1R activation occurs via direct binding of histamine to the receptor expressed on the surface of mast cells (60). Compounds inhibiting the docking to or, in general, the activation of NK1R should therefore posses the capability to alleviate itch sensation. Accordingly, the NK1R antagonist BIIF 1149 CL effectively decreased scratching behaviour in a mouse model of AD (61). But still the complex role of neuropeptides in pruritic AD is in need of further decipherment.

Acetylcholine

Over the past years, acetylcholine (ACh) emerged to become part of the choir of itch elicitors. As a major neurotransmitter in the autonomic nervous system, ACh exerts its action via binding to muscarinic (M1–M5) and nicotinic receptors. Cultured human keratinocytes which as well express muscarinic receptors indeed are also targeted by ACh. *In vitro*, this agent is synthesized, released and degraded by human keratinocytes in an autocrine, paracrine and endocrine mode (62–64). It has been shown in mice that carbachol and bethanechol, two muscarinic agonists, by activation of cutaneous M3 type receptors provoked itch sensation (65). In humans, elevated ACh expression was found in skin samples of AD patients indicating a role for this agent in the neurophysiology of pruritus (66).

In psychophysical experiments with humans, application of ACh induced pain more often than itch. This observation could be explained by the capability of ACh to activate neuronal 'itch units' along with a considerable amount of nonitch receptors which suppress the itch sensation and pain is perceived (67). In contrast, intradermal injection of ACh in lesional AD skin evoked pruritus instead of pain (38, 68, 69). It is thought that this itch-induction is obtained by a cholinergic mechanism, independent of histamine. But then a central sensitization for itch in patients with AD was recently discovered (70, 71) giving an alternative explanation at hand: injection of ACh along with a painful stimulus and the conversion of the pain sensation into a pruritic sensation on the spinal level could cause the itch sensation.

Tryptase

Stimulation of mast cells and keratinocytes not only release histamine but also tryptase, an agent that has a long history for being suspicious of accomplishing pruritogenic actions (72). In 1988, it was shown that intradermal administration of this agent into rabbit skin produced vasodilatation, erythema and pruritus (73). The complex mechanism that is subject to this phenomenon was decoded in parts only recently. An important observation for this clarification was that peripheral sensory nerve endings express a broad variety of receptors that are involved in inflammation. Simultaneously, it has been known for decades that acute or chronic skin inflammation lowered the threshold for pruritic stimuli, and thus caused peripheral itch sensitization (71, 74). One of the key receptors in neurogenic inflammation is the proteinase-activated receptor 2 (PAR_2). Upon demonstration that tryptase activated PAR_2 and that by this mechanism cellular effects were mediated which triggered the hallmarks of neurogenic inflammation oedema, plasma extravasation and recruitment of leucocytes (75), PAR_2 aroused the suspicion of being an 'itchy receptor'. This thesis was then further nurtured by a more recent study where not only an enhanced expression of both tryptase and PAR_2, on sensory nerves during AD was

detected but also the triggering of itching in AD patients by PAR_2 agonists was demonstrated (76). It is not clear to date whether the remaining PAR family members, foremost PAR_1 and PAR_4, are also involved in the itch pathway, and under which circumstances proteases may induce pain, inflammation or pruritus in patients suffering from AD.

Mrgpr

Several G protein-coupled receptors have been shown to act as key receptors in generating itch including histamine receptors and PARs. This group has been extended by the work of Liu et al. (77): Mrgprs (also termed Mrg/SNSR) are orphan receptors grouped into several subfamilies (MrgprA1–A22, MrgprB1–B13, MrgprC1–C14 and MrgprD–G). Mouse genome analysis revealed an existence of more than 50 members distributed to these subfamilies. The function of Mrgprs *in vivo* was so far an enigma but it was known that the expression of *MrgprA*s, *MrgprB4*, *MrgprB5*, *MrgprC11, and MrgprD*, is restricted to subsets of small-diameter sensory neurons in DRG and trigeminal ganglia (78, 79). To unveil the Mrgpr function, targetet deletion of an *Mrgpr* gene cluster located on mouse chromosome 7 was performed. *Mrgpr-cluster*$\Delta^{-/-}$ mice were then challenged with pruritogenic agents. Histamine and compound 48/80 induced itch behaviour in Wildtype mice and *Mrgpr-cluster*$\Delta^{-/-}$ mice of similar intensity. Strikingly, chloroquine, an anti-malaria drug that is known for pruritic side-effects, elicited itch in wildtype mice only (77). The group could show that the essential receptor to mediate the itchy action of chloroquine is MrgrpA3 and that chloroquine-sensitive neurons (3–4% of total DRG neurons) also respond to histamine and capsaicin. Interestingly, the human Mrgpr family member MrgprX1 shares a similar expression pattern with mouse MrgrpA3 (80) and also responds to chloroquine treatment indicating a role for this receptor in nonhistaminergic itch transmission in humans. But still it will be interesting to see how these findings translate to the human situation: chloroquine induced itch is common among black Africans but less common among other races (81). Still there is no doubt that the putative itchy action of MrgprX1 and its importance in the pathophysiology of pruritic diseases such as AD will be investigated soon. Alongside, it is tempting to speculate which endogenous agonist(s) activate this subset of MrgprX1-positive primary sensory fibres in the skin and whether an imbalance of its/their expression might affect the outcome of chronic pruritus. Certainly the discovery of Liu et al. may establish the ground for novel anti-itch drugs targeted against itch-selective neurons.

Cutaneous neuroreceptors and mediators: suppresion of pruritus

Endovanilloids and the TRPV ion channel family

Endovanilloids interact with TRPV1, an ion channel that belongs to the superfamily of transient receptor potential (TRP) channels. To date, six groups of molecules complete this superfamily: the canonical (TRPC), the melastatin (TRPM), the polycystin (TRPP), the ankyrin transmembrane protein 1 (TRPA), the mucolipin (TRPML) and the vanilloid (TRPV) subfamilies. All members of this superfamily act as nonselective calcium-permeable sensory transduction channels (82). Endovanilloids constitute a group of itch mediators to which heterogenous agents such as eicosanoids, histamine, bradykinin, ATP and various neurotrophins (NTs) (83–86) belong where all agents share endovanilloid functions (87). These agents either directly and/or indirectly activate/sensitize TRPV1 (84, 88, 89).

Originally, TRPV1 was found to be expressed by nociceptive sensory neurons (89) as an integrator of different pain-inducing stimuli. Its most well-known activator is capsaicin, the pungent ingredient of hot chili peppers. Administration of this compound excites (88) but then desensitize sensory afferents via TRPV1 activation, a mechanism that is utilized to alleviate pain and itch in numerous skin diseases (88, 90–92). More precisely, vanilloid administration leads to a depletion of neuropeptides in the C-fibres, which disrupts the communication between mast cells and skin sensory neurons (91–93). Interestingly, also the calcineurin inhibitors tacrolimus (94) and pimecrolimus (95) bind to TRPV1 suggesting a mode of action for these clinically important compounds.

Only recently, functional TRPV1 channels were reported on numerous nonneuronal cell types (96–98), including human epidermal and hair follicle keratinocytes, endothelial cells, dermal mast cells and dendritic cells (99–102). TRPV1 activation resulted in the release of pruritogenic cytokine mediators from several of these nonneuronal cells. In keratinocyte, TRPV1 was furthermore reported to mediate proliferation, differentiation and apoptosis, respectively (103, 104) but recent results utilizing a functional approach with both systemic and local resiniferatoxin (RTX) treatment question a functional expression of TRPV1 in primary human keratinocyte (105). It will be a subject of further detailed research to show whether endovanilloid itch mediators, besides acting on their cognate receptors, activate/sensitize TRPV1 expressed on itch-mediating sensory neurons only or also address TRPV1 expressed on other skin cells since the specificity of current antibodies against TRPV1 are questionable. In other words, topically applied capsaicin may not only desensitize TRPV1-mediated signalling in neuronal cells but may also provoke same in the many other skin cells to counteract a pruritogenic outcome.

Next to TRPV1, itching sensitization might also be related to the activation of other TRPs expressed in the skin, sensory fibres and keratinocytes including TRPV2, TRPV3, TRPV4, TRPA1 and TRPM8 (106) (Fig. 2). In fact, an important role for TRPV3 in pruritus has been shown recently. Asakawa and colleagues discovered an amino-acid substitution (G573S) in TRPV3 that led to an increase in ion channel activity in keratinocytes which caused a spontaneous allergic and pruritic dermatitis in mice (107).

Cannabinoids

Another suspect in the itch department is the cannabinoid system. Cannabinoid receptor-1 (CB1) is co-localized with

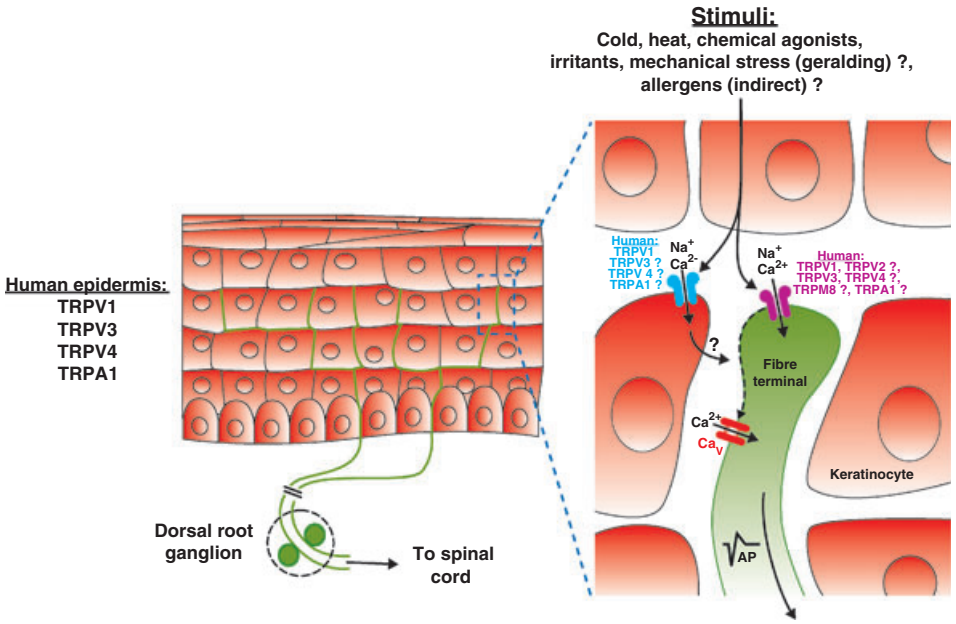

Figure 2 Potential role of transient receptor potential (TRP) channels mediating pruritogenic stimuli in the skin. Thermal, chemical and mechanical stimuli can stimulate sensory nerve endings and/or keratinocytes via TRP channels. Free sensory nerve endings are located in the skin (left) and are transmit pruritic and/or painful stimuli via the dorsal root sensory ganglia and the spinal cord for further information processing to the contralateral side of the CNS. Physical as well as chemical stimuli can directly activate TRP channels on free sensory nerve endings thereby causing depolarization of these fibres and the generation of specific action potentials (right panel). TRPV1, TRPV3, TRPV4 and TRPA1 are expressed in human keratinocytes, from which signals (which are not well characterized as of yet) are transduced to the DRG neurons (modified from Ref. 260).

TRPV1 in sensory neurons (108) and cannabinoids interact with the TRPV1-signalling pathway. This interaction triggers a switch of their neuronal effect from inhibition (109) to excitation and sensitization (110) under inflammatory conditions. In fact, a topically applied synthetic cannabinoid, HU210, suppressed histamine-induced pruritus and reduced axon reflex erythema (111). CB1 as well as CB2 were also found to be expressed in nonneuronal cells of the skin such as mast cells (112, 113). In consequence, cannabinoid receptors may be involved in the neuronal–nonneuronal cellular network of pruritogenic stimuli arising in/from skin. In addition, these findings support an antipruritic role of the cannabinoid system which could be exploited for new therapy approaches in itch-accompanied skin diseases. In fact, preliminary studies with a cannabinoid (palmitoylethanolamin) containing cream assign anti-inflammtory and antipruritic properties to this compound in AD (114). A very appealing consideration for administration of cannabinoid in itch therapy is the possibility of co-administration with a TRPV1 agonist. Thereby, the patient would benefit from (i) the antipruritic impact of both agents and (ii) the mitigative effect of the cannabinoid on an acute burning sensation that is elicited by exclusive capsaicin administration.

Opioids

It is a common habit to counteract itch by scratching. To be more precise, itch is counteracted only by a painful stimulus. In experimental settings, this painful stimulus can be mimicked by various painful thermal, mechanical and chemical stimuli (115). For instance, it is well demonstrated that electrical stimuli can reduce an itch sensation for hours (116). The potency of itch-inhibition though appears to be dependent on the nature of the applied stimulus: noxious heat stimuli and scratching produce a stronger itch inhibition than noxious cold stimuli (117). Conversely, it is imaginable that analgesia may reduce the competence of pain to inhibit itch whereby pruritic sensation is amplified (118). This phenomenon is observed when μ-opioid receptor agonists are spinally administered as segmental pruritus arouses along with the desired segmental analgesia (119–125). Accordingly, opioid receptor antagonists may have antipruritic effects in pruritic diseases (126–132). The pruritic μ-opioid receptor is expressed by C-fibres. During pain perception, μ-opioid receptor antagonists such as naxolone are not ideal antipuritics because such compounds can reverse opioid analgesia concurrently (133, 134). However, a combination of high-dose intrathecal opioids with postoperative intravenous naloxone provided excellent analgesia with minor pruritic side-effects (135).

The antipruritic κ-opioid receptor (KOR), expressed by Aδ-fibres, seems to be a more promising target to ameliorate itching after spinal analgesia administration without engaging in the desired antinociception (136). When treated chronically with U-50488H, a selective KOR agonist, treated monkeys displayed an excessive scratching activity upon agonist-withdrawal (137) indicating an antipruritic role of KOR

when holding in mind that many withdrawal symptoms from opioids appear to be opposite to the acute effects of the administered agonist (138, 139). In another pharmacological monkey study, KOR agonists prevented/reversed intrathecal morphine-induced itch/scratching responses without interfering with intrathecal morphine analgesia (140). This outcome led to a clinical trial of a new KOR agonist, nalfurafine (TRK-820), in hemodialysis patients suffering from uraemic pruritus resulting in a successfull amelioration of the itch sensation in these patients indicating an important therapeutical potential of KOR agonists as antipruritic agents (141).

In patients with pruritic AD, the itchy pathogenesis of the disease might in parts be ascribed to the involvement of opioids because β-endorphin serum levels were found to be markedly elevated (142).

To date, not much is known about a participation of opioid-receptors in the neuronal–nonneuronal cellular network of pruritogenic stimuli. It has been speculated though that downregulated epidermal μ-opiate receptor of AD patients increases the pool of available opioid ligands, which then in turn induce histamine-unrelated chronic pruritus (143, 144).

Cytokines and inflammatory cells

Under inflammatory conditions, cytokines are, among numerous other factors, released from cutaneous and immune cells. Some of these cytokines are well capable of triggering pruritic sensations and release of neuropeptides from sensory nerves. In the following, such cytokines will be briefly described.

Interleukins

Although the contribution of many interleukins in atopic and allergic diseases is well established, the precise role of these immune mediators in pruritus is still unclear. For instance, a pleithropic inhibition of cytokine production achieved by usage of cyclosporine A resulted in the mitigation of itch in patients suffering from AD (145, 146). Also, upon prick testing, supernatants of mitogen-stimulated leucocytes were pruritic in AD patients but not in controls (147). Cyclosporin A (CyA), among other interleukins, effectively blocks the production of IL-2. Gaspari and co-workers showed that actually this distinct interleukin is a potent activator of pruritus. In their study, all cancer patients treated with IL-2 developed macular erythema with burning sensation and cutaneous pruritus (147). In AD patients, as well as in healthy individuals, a single intracutaneous injection of IL-2 resulted in a low-intensity intermittent local itch perception (148, 149). It has been demonstarated that bradykinin is involved in the mechanism to modulate the intensity of IL-2-induced pruritus on sensory nerves (150) but the mechanism for the induction of itch by IL-2 itself remains to be uncovered. Because the pruritogenic response initiated by IL-2 administration is faster in AD patients than in healthy individuals, an indirect mechanism of action via other mediators is likely. Recently, a role for IL-8 in the pathogenesis of pruritus was postulated. Enhanced level of this chemokine was detected in lesional skin (151), plasma (152) and blood mononuclear cells (153, 154) of AD patients. In addition, these findings indicate a role for IL-8 in the generation of pruritus but so far no study provided direct evidence for this thesis. Future research has to clarify the connection of IL-8 and 'itchy outcome'. A novel T-cell-derived cytokine was reported to induce severe pruritus and dermatitis in transgenic mice: IL-31. Its targeted receptor to initiate itch was shown to consist of a heterdimeric receptor composition of IL-31 receptor and oncostatin receptor (155) and to cause pro-inflammatory effects of activated human monocytes and macrophages which may have implications for cutaneous inflammation in eczema (156). Subsequent to this initial study, IL-31 was also found to be overexpressed in pruritic atopic skin (157). Especially in patients with prurigo nodularis, one of the most pruritic forms of chronic skin inflammation, IL-31 levels were severely upregulated. Also a role for IL-31 in the pruritus of atopiform dermatitis is under consideration (158). *In vivo*, staphylococcal superantigen rapidly induced IL-31 expression in atopic individuals indicating a new link among staphylococcal colonization, subsequent T-cell recruitment/activation and pruritus induction in patients with AD.

Interferon gamma (IFN-γ)

While long-term treatment with IFN-β appears to cause pruritic side-effects (159), IFN-α seems to have a beneficial effect on pruritus in various diseases (160–162). In patients suffering from AD, IFN-γ treatment effectively relieved pruritus (163). This relief was reported by AD patients to still exist after long-term treatment with IFN-γ (164). The distinct mechanism of action for IFN-γ to modulate pruritus, however, has still to be identified. It is likely that the diminished IFN-γ production in peripheral blood mononuclear cells of AD patients (165) accounts for the pruritus phenomenon.

Neurotrophin-4

Recent studies suggest a contribution of NT-4 to inflammatory and itch responses of patients with AD. NT-4 is produced by keratinocyte and highly expressed under inflammatory conditions and acts growth-promoting 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 (166). Interestingly, IFN-γ, itself a potent anti-pruritic agent, can initiate NT-4 production. These findings suggest a close link between immune and neurotrophic factors in the development of pruritus in AD.

Eosinophils and basophils

The role of eosinophils in the pathogenesis of AD is well established but how they engage in the pathophysiology of pruritus during AD is still unclear. It is likely that factors released by eosinophils such as prostanoids, kinins, cytokines, leucotrienes, platelet-activating factor and proteases adopt the pruritogenic effect of eosinophils on a molecular level (167–172). But it is also imaginable that the itch reponse is elicited indirectly by activation of mast cells which in turn

trigger the release of histamine or proteinases from eosinophils. In summary, although some reports are in favour for a role of eosinophils during pruritus in various diseases (167, 170, 172), direct evidence for a role of eosinophils for itch responses during AD is still lacking. Peripheral blood basophils are inconspicuous in patients suffering from AD. However, *in vitro* analysis of basophil function demonstrated faster histamine releasability upon stimulation (173, 174). These *in vitro* results could not be confirmed in patients with AD, though (175). The contribution of basophils to the development of itch and erythema in patients with AD is still in need of detailed investigation.

Platelet-activating factor

The lipid mediator Platelet-activating factor is a component of several inflammatory cells such as mast cells and granulocytes with proinflammatory activity (176). One of its actions upon intradermal injection is to increase vascular permeability and thereby to cause a wheal and flare reaction along with pruritus. The underlying mechanism debated is based on an indirect pruritogenic effect via histamine release (177). Platelet-activating factor antagonists have proved, in a double-blind study, to be able to reduce pruritus in AD patients when applied topically already within the initial weeks of treatment (178).

Leukotriens

Leukotriens are mediators with proinflammatory properties generated from arachidonic acid, an essential fatty acid found in the membrane of all cells (179). A synthesis pathway whose key enzyme is 5-lipoxygenase provides all known leukotriens. Their cellular origin is reflected by 5-lipoxygenase expression and essentially restricted to various myeloid cells such as neutrophils, monocytes/macrophages, B lymphocztes and mast cells. Leukotriens bind to three receptor subtypes: BLT, $CysLT_1$ or $CysLT_2$.

The contribution of leukotriens to the pathophysiology of inflammatory diseases, in particular asthma, is well established whereas their role in the pathogenesis of pruritus is still subject of debate. However, intradermally injected leukotriene B4 was demonstrated to provoke scratching in mice (180) and high urinary leukotriene E4 levels could be correlated to nocturnal itch (181). An increased abundance of leukotriens could therefore account for itch induction in AD. In fact, inhibition of leukotrien receptor by zafirlukast and zileuton resulted in a reduction of pruritus in patients with AD (182–184).

Trigger factors aggravating pruritus perception in atopic dermatitis

The skin of AD patients reveals a higher tendency to itch upon minimal provocation because of reduced itch threshold and prolonged itch duration to pruritic stimuli as compared with healthy skin (185–187). A series of pruritus triggering factors are known (186), which release mast cell mediators or vasomotor and sweat reactions to cause itch, and all may be subjected to emotional influences (185).

Scratching

It is a recurring debate whether scratching itselfs precedes the induction of AD or if itch and scratching are a consequence of the presence of eczemas. The final answer to this debate is indeed not found so far, in particular the itch–scratch order crucial for the pathophysiology of AD remains to be an enigma. However, results obtained from an animal study were in favour of scratching behaviour anteceding and thereby contributing to the development of dermatitis (188). This AD mouse model investigated the development of spontaneous dermatitis by comparison of mice neonatally treated with capsaicin (Cap-NC mice) to ablate capsaicin-sensetive sensory nerves or vehicle. In the treated mice, scratching behaviour was hardly observed and the development of dermatitis determined by elevation of the serum IgE level and the numbers of infiltrating eosinophils and mast cells was significantly suppressed. Also the capability of spleen T cells to produce both T-helper Th1 (IFN-γ) and Th2 (IL-5, IL-13) cytokines appeared to be constrained in Cap-NC mice, indicating a direct correlation of scratching and subsequent immunological responses. Clinically, the prevention of itch sensation and/or itch-associated scratching behaviour may be an additional important step in the treatment of AD.

Epidermal barrier

Xerosis is a common problem of the skin of patients suffering from AD. It constitutes a keratinization disorder that reflects a dysfunctional epidermal barrier. This dysfunction results in an increased transepidermal water loss and a decreased ability of the stratum corneum to bind water (189) which may be due to incomplete arrangement of intercellular lipid lamellae in the stratum corneum (190, 191). It is well-established knowledge that a disturbed epidermal barrier constitutes an activator of pruritus. In fact, scratching behaviour and induction of pruritus are triggered by water content below 10% (192). The precise mechanisms for the pruritogenic effect of a disturbed epidermal barrier remain unknown. One possibility may be that an impaired skin barrier simplifies the penetration of irritants and itchy agents (193, 194). Animal studies demonstrated that the epidermal barrier homeostasis and stratum corneum integrity is furthermore affected by psychoemotional stress: decrease of lamellar bodies' formation and secretion along with decrease corneodesmosomes production was observed (195). These findings suggested a correlation between stress factors and decreased barrier function and might be of relevance for patients with AD (see Stress section).

Stress

It has long been appreciated that both acute stress and chronic psychoemotional stress can trigger or modulate pruritus (196–203).

To understand this correlation requires a deeper understanding of the neuroendocrinology and neuroimmunology of stress responses. Stress responses are learned, involve the cortical centres but can be reprogrammed by behavioural

and neuropharmacological/neurendocrine therapy. In patients with AD, a close relationship between psychological factors, pruritus and scratching has been shown (198, 199, 204–206) – intriguing 81% of AD patients attribute emotional stress to aggravate their pruritus (46). In turn, an experience of increased itch upon stressful events might lead to conditioned itch in AD patients, which thereby could give way to a vicious circle of aggravation and perpetuation of stress-induced itch. Relaxation therapies that are also operant for pain patients like autogenic training or hypnosis have been found to ameliorate itch and eczema in AD patients by distinctly treating mental stress factors (207, 208). The mechanism of stress-induced pruritus in AD patients is not unravelled as of yet but an activation of the psycho-neuroendocrine system seems likely (198, 199). For instance, immobilization stress applied to rats resulted in mast cell degranulation (209) supporting the thesis that stress tension may lead to increased release of pruritogenic mediators from mast cells in AD patients which further may results in intensified scratching behaviour and subsequent skin lesions (199). In another study, AD patients undergoing a stress test revealed a responsive increase of IgE, blood eosinophils, IFN-γ and IL-4 (210). Pruritus intensity may be modulated by vasodilators responses and increased skin temperature in consequence to emotional stress (185, 211).

Sweating

Generalized itching evoked by any stimulus to sweating (thermal, emotional stimuli) is a typical hallmark and represents the most common trigger factor of itch in patients with AD (185, 212, 213). Increased sweating was observed in lichenified skin of patients with AD. Causative factor might be a lowered threshold for sweat stimulation in chronically pruritic and altered skin (214). The exact mechanism underlying sweat-induced pruritus is far from being resolved, but recent evidence points to a role of ACh. ACh-induced eccrine sweating (215), is found to be increased in the skin of AD patients (64), and finally acts as a sensitizer or pruritogenic in AD patients (68).

Microcirculation

Clinically, itching is mostly associated with erythema and hyperthermia. A variety of mediators for itching such as histamine, tryptase, ACh, SP, prostaglandins are potent vasodilatators, rarely vasoconstrictors (NPY or catecholamines). Neuropeptide-induced itching does not vary between atopic and nonatopic patients, whereas vascular responses obviously show a significant difference between these two groups. Moreover, patients with AD were more susceptible to stress and showed increased vasodilatation as compared with controls (216). Pruritic mediators which also acts as potent vasodilatators may be histamine and tryptase. Certain prostanoids are effective sensitizers and vasodilatators. In sum, which receptors are the most important ones to regulate itch and vasodilatation among the different pruritic diseases is still a matter of debate.

Exogenous factors

Pruritus elicited by direct contact with wool in patients with AD is a characteristic and reproducible phenomenon (217, 218). It is likely that the irritation is caused by the spiky nature of wool fibres itself. Mechanical vibration seems to be irrelevant for induction of itch because it inhibits experimental, histamine-induced itch (219). Interestingly, thicker wool fibres were found to provoke more intense itching than thinner fibres (220). Other irritants like lipid solvents, disinfectants (221) may additionally contribute to aggravate xerosis. Contact- and aero-allergens as dust mites or pollens (212) may also provoke pruritus. Microbiological agents like bacteria (*Staphylococcus aureus*) or yeast may exacerbate both dermatitis and pruritus (186, 212).

Pruritus and erythema may be also triggered by exogenous substances like proteinases from bacteria and dermatophytes increasing blood flow, conduct vasodilatation or release histamine. Among those, heat, hot and spicy foods, hot drinks and alcohol are most likely to generate itch in AD patients (186, 212, 222). In early childhood, food allergies exacerbate eczematous skin lesions, but these food allergies mostly resolve during ageing in older children and adults (222).

Management of pruritus in allergic and atopic skin diseases

The handling and treatment of severe itch is one of the major challenges in the management of patients with allergic and AD (Table 2). Concerning a successful suppression of pruritus, several levels have to be considered. First of all, identification and elimination of individual trigger factors must be appreciated as the primary goal of the management (200, 223). As patients frequently develop some harmful self-treatments, e.g. alcohol-containing solutions, these misconceived therapies must be eliminated. Lotions and creams lubricating the skin have to be recommended. To combat skin dryness, application of hydrophilic emollients and bathing with oily bath additives is additionally helpful (223). Lipid based repair formulations based on ceramide-dominant contents have been described to be superior in reduction of disease severity (224–226). Adding substances such as urea, menthol, camphor and polidocanol to these cremas leads to an immediate short-term interruption of the itch. These creams can be applied by the patients each time the itch starts to worsen (227). Unspecific physical modalities are described to be beneficial like acupuncture (228) and cutaneous field stimulation (116).

Another level of therapy is the handling of the scratch artefacts. Chronic pruritus induces chronic scratching or rubbing. Accordingly, erosions, ulcerations, bleding, crusts, lichenifications up to prurigo nodularis may develop. Stage-dependent, disinfections, antimicrobials and topical corticosteroids have to be applied. In patients with prurigo nodularis or lichen simplex associated to AD, frequently an automatic scratching behaviour develops. These patients additionally need education to control scratch behaviour (229). For example, the behaviour method ‘habit reversal’ can be employed (230). First, patients become aware of their scratching behav-

Table 2 Therapeutic strategies alleviating pruritus in atopic dermatitis

Therapeutical modalities	Examples
Elimination of trigger factors	Perspiration, xerosis, emotional stress, scratching, wearing wool fibres, using of mild soaps, detergents, hot, spicy food, hot drinks, alcoholics
Skin barrier protection and restauration, itch control	Emollients
	Bathing with oily additives
	Lotions, creams or sprays containing menthol, local anaesthetics, camphor, polidocanol, urea, pimecrolimus, cooling
	Skin care to reduce sweating-induced itch
Therapy of scratch artefacts	Desinfection, antibiotics, topical steroids, pimecrolimus, tacrolimus, doxepin cream 5%, amitryptiline 4% / ketamine 2% cream
	Interruption of itch-scratch-cycle: behaviour therapy against scraching
	Physical exercise
	Acupuncture, hypnosis
	Cutaneous field stimulation
Symptomatic therapy: anti-inflammatory therapy	Corticosteroids, topical and systemical
	Cyclosporin A
	Tacrolimus, pimecrolimus
	(Interferon gamma)
	Immunoglobulin therapy
	Ultraviolet irradiation (UVA1, UVA/UVB)
Symptomatic therapy: interfering with pathophysiology of pruritus in AD	μ-Opioid antagonists, κ-opioid agonist
	Capsaicin
	Cannabinoid agonists combination of high-dose antihistamines (neurokinin-1 receptor antagonist)
Contradictory results	Antihistamines, leukotriene antagonists
	Doxepin (potential: contact allergy upon long-term application)
	Mycophenolat mofetil
Systemic therapy	Gabapentin, pregabalin

iour by counting scratch movements. In a second step, they learn a new behaviour by reacting to scratch impulses. Scratch-induced skin damage caused by nocturnal scratch movements may be improved by using cotton gloves. Also controlled physical exercise like gymnastics or ball games were demonstrated in a controlled study to teach patients to cope better with itch attacks (231).

As chronic scratching represents also a trigger factor and maintains the itch-scratch-cycle, the most important step in the management of the AD patients is the interruption of itch by an effective symptomatical topical and/or systemical therapy.

Symptomatical topical and systemical therapy

Studies concerning the pathophysiology of pruritus clearly demonstrated that different nociceptive mechanisms are involved in AD. Thus, conventional therapeutic modalities like antihistamines often fail to ameliorate pruritus in AD (33). This is comprehensive with the idea that histamine is not the major mediator of pruritus in AD (35). Placebo-controlled studies concerning the antipruritic effect of oral antihistamines have shown conflicting results in AD. In some studies, no superior effect was observed as compared with placebo (232–234) whereas others showed a significant antipruritic effect (38, 235–237). In recent experimental studies, the H1-antihistamine cetirizine could be demonstrated to focally reduce itch (38). However, an evidence-based review concerning the efficacy of antihistamines in relieving pruritus in AD concluded that little objective evidence exists for H1-antihistamines to demonstrate improvement of pruritus (33). Topical application of the tricyclic antidepressant *doxepin* suggested to have antipruritic effects because of its high affinity to H1 histamine receptors. In fact, 5% doxepin cream revealed improvement of histamine-induced and SP-mediated cutaneous responses but also evoked sedative effects in some patients (238, 239). Unfortunately, doxepin was accompanied by contact allergies after long-term application (240).

In general, anti-inflammatory, immunomodulating therapies as regularly applied in AD often result also in cessation of pruritus, because they suppress the inflammatory mechanisms underlying the induction of itch. So far, most effective and consistent antipruritics remain systemic immunomodulators such as glucocorticoids, CyA, tacrolimus, pimecrolimus and ultraviolet radiation therapy (146, 241–244). Moreover, there are no evident and efficient alternatives to topical application of *corticosteroids* or calcineurin inhibitors for the control of acute episodes in AD (244–246). With reduction of skin lesions, a decreased itch intensity results probably because of reduction of inflammatory cells and protection of depolarization of nerve fibres mediated directly by the steroid (247). However, treatment of a patient suffering from amyloidosus lichen (LA) associated with AD by a combination of narrowband ultraviolet B phototherapy, topical corticoster-

oids and an oral antihistamine led to an improvement of AD as well as LA symptoms (248). *Cyclosporin A*, a cyclic polypeptide with potent immunosuppressive effects, has been reported to have a considerable itch-reliving effect in various diseases including AD. In a randomised study, CyA was demonstrated to significantly reduce itch intensity (146). After discontinuation of this therapy, pruritus recurred immediately. As oral CyA has demonstrated to be effective in AD, a topical CyA formulation has been developed to avoid systemic adverse effects. However, no significant improvement of AD was found upon clinical application (249).

Recently, much interest has been drawn to *tacrolimus and pimecrolimus*, both effective immunomodulators and calcineurin inhibitors. Although the mode of action is similar to that of CyA, the molecular weight is lower and its potency of inhibiting T-cell activation is higher. Multiple, large randomised studies of the last years confirmed topical administration of tacrolimus and pimecrolimus to interrupt acute attacks of AD, reduce fastly pruritus and prevent exacerbation after cessation of eczemas in adults and even children with AD (250–253). This beneficial effect of pimecrolimus is also detected in children suffering from Netherton syndrome (254). Upon treatment with a 1% pimecrolimus cream, rapid marked improvements were observed in the Netherton Area and Severity Assessment, Eczema Area and Severity Index, and pruritus scores. Treatment with *IFN-*γ has been shown to be effective not only for the improvement of erythema, excoriations and lichenifications, but also of pruritus (164, 255, 256). In addition, this effect maintained up to 2 years after therapy (164). Amelioration of pruritus has also been described under intravenous *immunoglobulin* therapy in few cases of AD (257, 258). As of yet, however, no controlled studies were performed.

Also other therapeutical modalities such as TRPV1 receptor antagonists/or agonists (90, 259), μ-*opiate receptor antagonists* (128–130), κ-opioid receptor agonists, PAR_2 receptor antagonists, histamine-3 receptor or histamine-4 receptor targeting molecules, cannabinoid agonists, nerve-growth factor or nerve-growth factor receptor antagonists, neurokinin-1 receptor antagonists, GRPR antagonists, certain prostaglandin and *leukotriene antagonists* (182–184) appear to be promising new approaches for the therapy of AD and certain allergic diseases, but will have to prove their safety and practicability in further controlled studies. In conclusion, the pathopysiology of pruritus in AD has not been evaluated completely. Accordingly, no specific antipruritic agent has been developed and management of itch in AD is confined to mainly immunomodulating therapies. However, the consideration of several levels may improve this distressing situation for the patients. Further investigations are necessary to establish antipruritic substances influencing the centrally and peripherally altered itch perception to interfere with the complex pathophysiology of pruritus in AD.

Conclusion and perspectives

Amelioration of pruritus is a major goal in the treatment of patients suffering from allergic and atopic skin diseases. Identification of a single effective pharmacological treatment is an old continuing demand of physicians handling and managing itch symptoms for this disease. Promising new approaches have been made, but recent insight into the origin and onset of pruritus leads to the conclusion that the single treatment/compound that universally combats the itch symptom in AD patients may not be found in the near future. Because itch pathophysiology is too complex involving neurophysiological and neuroimmunological aspects, more has to be learned about the mediators, receptors, multidirectional pathways in the near future to reach a valid golden standard for therapy. However, the complexity of interactions between the central and peripheral nervous system and the skin in generating this symptom has catapulted an indeed broad but clearly delineated spectrum of molecular targets into focus which, when successfully exploited, could serve to treat the itch perception in AD patients. Once these molecules will be explored systematically and in detail, we undoubtedly will hold sophisticated and more effective therapeutic strategies for pruritus management in AD in our hands. In particular, combining approaches that target both the peripheral production of inflammation-induced itch signals and the peripherally driven cycles that perpetuate itch and provoke spinal and central sensitization to itch in AD are promising new strategies. The direction of the development of innovative and more effective itch management is to unequivocally extend the scope of pharmacological targets far beyond the ubiquitous usual suspect histamine.

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