Pathophysiology of itch and new treatments

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Current Opinion in Allergy and Clinical Immunology 2011, 11:420–427

Purpose of review

Itch represents one of the most bothersome symptoms in allergic disorders and numerous dermatological and systemic diseases. Chronic itch has a dramatic impact on the quality of life. The pathophysiology of itch is diverse and involves a complex network of cutaneous and neuronal cells. Thus, we highlight the current pathophysiological aspects of itch together with new treatment options.

Recent findings

Apart from histamine, several mediators and receptors including the neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor, neurokinins/neuropeptides such as substance P, gastrin-releasing peptide, cytokines such as interleukin-31, autotaxin and the histamine H4 receptor have been identified for playing a role in the pathophysiology of itch. In the skin, tissue resident cells such as keratinocytes, mast cells and cells of the inflammatory infiltrate including lymphocytes and eosinophils have been described to interact with neuronal cells, for example via the release of neurotrophins, neuropeptides and cytokines, adding novel regulatory pathways for the modulation of itch. Accordingly, promising treatment strategies such as the neurokinin-1 receptor antagonist aprepitant have been introduced for a successful management of itch.

Summary

In this review, we highlight novel key players in the pathophysiology of itch with subsequent introduction of promising, novel and experimental treatment strategies.

Keywords

atopic dermatitis, eosinophil, interleukin-31, itch, mast cell, pruritus

Curr Opin Allergy Clin Immunol 11:420–427

1528-4050

Introduction

Itch represents one of the most bothersome symptoms, which almost everyone has experienced once in the lifetime. According to the International Forum for the Study of Itch, itch is defined as being chronic if it persists for 6 weeks or longer [1]. Chronic itch can occur in all ages. However, children may be less affected because they also display a significantly lower number of comorbidities, which are known to evoke itch. Itch triggers the desire to scratch. Next to pain, itch may serve as an alarm system for the skin in order to remove possibly damaging or harming substances quickly by the triggering of scratch. Thus, acute itch fulfils an essential part of the innate defence mechanism of the body. However, chronic itch – especially when present for years – lost this function.

In the skin, many factors contribute to the induction, exacerbation and inhibition of itch. For example, physical stimuli such as cold and heat modulate the perception of itch; painful heat and cold can significantly diminish itch, whereas moderate cold intensifies it [2]. Mechanical factors such as rubbing or scratching the skin can briefly suppress itch by activating nerve fibers that selectively activate and deactivate certain areas of the central nervous system [3].

Itch is mediated via free nerve endings of nonmyelinated C-type nerve fibres that are located at the dermoepidermal junction and within the epidermis. There is a subpopulation of itch-specific nonmyelinated C nerve fibres that respond only to histamine. Interestingly, there is also evidence of histamine-independent itch-specific fibers in the skin [4]. In this regard, specific G protein-coupled receptors, which mediate chloroquine-induced itch have been identified in peripheral sensory neurons [5]. These neurons also respond to other itch inducing signals including capsaicin. Further, spinal neurons express the gastrin-releasing peptide receptor, which has previously been shown to be importantly involved in the transmission of itch, indicating that receptor expressing neurons may be itch-specific [6].

Another key element for the transmission of itch are neurokinin-1 receptor expressing skin nerves and dorsal horn neurons as shown recently in a rat model, indicating that the neurokinin/neuropeptide substance P may play a role as a spinal transmitter for itch [7••].

Chronic itch is a major diagnostic and therapeutic problem and can have a profound impact on the patients' quality of life [8•]. Itch can occur in patients suffering from numerous different diseases, for example inflammatory skin diseases, metabolic disorders, liver and kidney diseases, or lymphoproliferative and myeloproliferative disorders. The underlying causes and the mechanisms of itch are diverse and only partly understood. A better understanding of the pathophysiology of itch will support the diagnosis and treatment options for patients with chronic itch.

Key points

- Itch is on of the most bothersome symptoms which can have a strong impact on the quality of life.
- Experimental and promising treatment strategies include the neurokinin-1-receptor antagonist aprepitant or the kappa-opioid agonist nalfurafine in patients with chronic severe itch.
- Knowledge of the underlying mechanisms and complex cellular interactions in the skin and nervous system will help us to identify novel treatment strategies, which are displayed by small case series of promising drug.

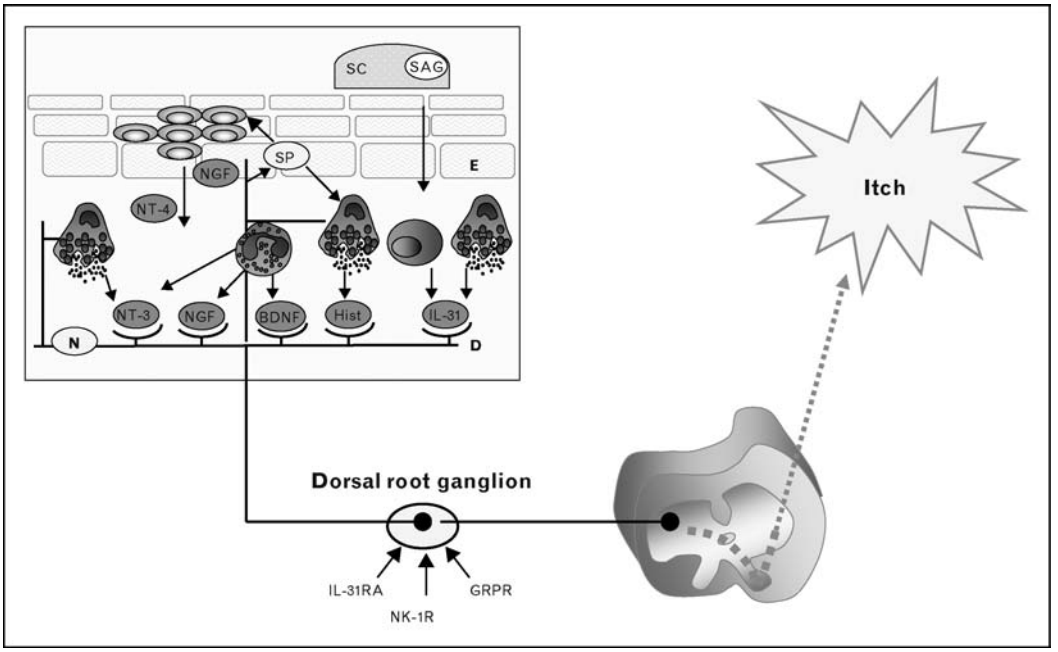
Pathophysiology of itch in the skin: the role of immune cells

The orchestration of itch in the skin appears to be regulated by a complex interplay of many factors and may differ depending on the pathophysiological changes in the skin. Itchy skin diseases, including atopic dermatitis, chronic urticaria, psoriasis and allergic contact dermatitis are associated with increased production and release of cytokines, neurotrophins and neuropeptides possibly leading to the exacerbation of itch [9]. Thus, infiltrating and tissue resident cells can, at least in part, be responsible for the induction or exacerbation of itch (Fig. 1).

Keratinocytes

As resident cells of the skin, epidermal keratinocytes provide an effective barrier against physical, chemical and biological environmental factors. Thus, keratinocytes are a crucial part of the innate defense system. As described before, induction of itch in the skin is an important defense mechanism to detect and instantly

Figure 1 Interplay between tissue resident cells and itch mediators in the inflamed skin



Neuroimmune interaction mechanisms orchestrate the phenomenon of itch. A complex interplay between keratinocytes, mast cells, T-cells eosinophils, superantigen-producing (SAG) staphylococcal colonies (SC) and nerves (N) in the epidermis (E) and dermis (D) of inflammatory skin disease leading to increased release of substance P (SP), nerve growth factor (NGF), neurotrophin (NT)-3, NT-4, brain-derived neurotrophic factor (BDNF), histamine (Hist) and interleukin (IL)-31. Dorsal root ganglion expressing receptors for IL-31 (IL-31RA), neurokinin-1 receptor (NK-1R) and gastrin-releasing peptide receptor (GRPR).

remove possibly harmful substances quickly from the skin by scratching. Therefore, the epidermis has to provide ways for detection of potential threats and for transmitting itch via the production and release of pruritogenic mediators. Further, epidermal keratinocytes are in close connection to sensory nerves within the epidermal part of the skin, assuming a direct interaction mechanism between both cell types (Fig. 1).

Keratinocytes release a battery of inflammatory and pruritogenic substances, which can be induced by various innate mechanisms, for example toll-like receptors, Ultraviolet (UV)-light or thermoreceptors [10]. Keratinocytes are able to detect itch-associated signals by expression of protease-activated receptor-2 [11], opioid [12], cannabinoid [13] and histamine H4 receptors [14]. By responding to these signals, keratinocytes can modulate itch in many ways. For example, keratinocytes can release neurotrophins including NGF [15,16] and neurotrophin-4 [17] (Fig. 1), lipid mediators [18] or endothelin-1 [19], which can either directly activate itch fibres in the skin or activate mast cells to release pruritogenic mediators. In addition, neuropeptides including substance P have been shown to significantly increase the release and production of NGF of human cultured keratinocytes, indicating a neuroimmune interaction mechanism between sensory nerves and keratinocytes [20] (Fig. 1). Interestingly, keratinocytes can also inhibit itch through the release of endocannabinoids, which bind directly to inhibitory receptors on sensory nerves [13]. The regulatory interplay between activating and inhibitory mechanisms of itch in specific disease via keratinocytes is, however, thus far not clear.

Mast cells

Mast cells are tissue resident cells, which are found in close vicinity to hair follicles, keratinocytes, blood vessels and sensory nerves [21]. Mast cells express a large number of receptors, which can activate the cells to release their mediators [22].

The best-known mast cell mediator for the induction of itch is histamine. Preformed histamine is present in large amounts in mast cell granules and thus, after cell activation, can be immediately released into the surrounding area in which it induces itch via H1 receptors on nerve fibres. Apart from H1 receptors, histamine appears to modulate itch also by H3 and H4 receptors. The pharmacological blockade of H4 receptors has been shown to significantly reduce itch in mouse models and diminish existing airway inflammation [14,23••]. In the skin, H4 receptors seem to be involved in the inflammatory process because H4 receptors acting on Th cells enhance the production of proinflammatory cytokines as shown in atopic dermatitis [24,25•]. H3 receptors appear to be involved in the suppression of pruritus because H3 receptor antagonists have been shown to induce pruritus in mice [26].

Apart from histamine, many other mast cell-derived substances have been identified to be involved in the induction or modulation of itch. For most of these substances, the clinical relevance remains, however, to be determined. Among these are proteases, lipid mediators, neuropeptides and various cytokines. Interestingly, skin mast cells of patients with psoriasis are also a source of interleukin (IL)-31, which has been identified for being a potent pruritogenic cytokine (Fig. 1) [27••]. Other substances that are not produced by mast cells have been shown to induce or exacerbate itch without directly affecting nerve fibres but through indirect effects as a result of mast cell activation in the skin. Although these are broadly referred to as histamine liberators, the activation of mast cells may also lead to the release of other itch-inducing substances. Among the most relevant mast cell activators in pruritic diseases are neurotrophins such as NT-3 [28], neuropeptides including vasoactive intestinal peptide, calcitonin gene-related peptide, substance P (Fig. 1) and endothelin-1 [19]. In this regard, it was shown in a mouse model that a mast cell-mediated allergic reaction is markedly diminished in the absence of sensory cutaneous nerves [29]. Together, many of the mast cell mediators are involved in the elicitation of itch. Thus, mast cells have a central role in the cellular network of itch.

Eosinophils

Itchy skin diseases including atopic dermatitis, allergic contact eczema, chronic urticaria and the scratch-related prurigo nodularis are associated by an increased cellular infiltration of eosinophils. Eosinophils are considered to be predominantly tissue resident cells and do not re-enter the circulation. In humans there are relatively few data on the kinetics of eosinophil trafficking and it is difficult to make firm statements about the relative contribution of eosinophilopoiesis and recruitment into the tissue [30]. Interestingly, eosinophils can be found in close vicinity to nerves [31].

Eosinophils constitutively express mRNA for NGF and NT-3 (Fig. 1) [32,33]. This is interesting, as neurotrophins are capable of inducing the cutaneous nerve sprouting and myelinization of nerves. Direct neuroimmune interactions between eosinophils and nerves have been shown in an in-vitro model in which stimulated eosinophils released NGF and induced neurite outgrowth, which was abolished by anti-NGF neutralizing antibodies [33]. Besides NGF, brain-derived neurotrophic factor (BDNF) contents are also higher in eosinophils of patients with atopic dermatitis compared with healthy controls and can be released accordingly [34,35]. This is of interest because increased BDNF levels correlate with

disease severity assessed by SCORing Atopic Dermatitis score in adults [36] and in children with atopic dermatitis, in which BDNF levels also correlate with scratching activities [37]. Interestingly, scratching behaviour and skin inflammation could be inhibited in a mouse model using the neurotrophin receptor antagonist for tyrosinkinase A receptor [38].

BDNF also induces chemotaxis of eosinophils in patients with atopic dermatitis, enhancing the recruitment of these proinflammatory cells in the tissue [35,39]. As expression of all neurotrophin receptors is significantly higher in eosinophils of itchy skin diseases such as atopic dermatitis compared with allergic rhinitis and skin healthy controls, the functional capability of neurotrophins may thus be explained by increased receptor expression [39].

Eosinophils have also been shown to express histamine receptors including the H4 receptor [40]. Furthermore, eosinophils can be a source of neuropeptides such as vascular endothelial growth factor, which might point toward a role in some pruritic skin diseases, possibly including urticaria [41]. Thus, the capability of eosinophils to respond to various trigger factors via the production of neurotrophins, neuropeptides and other cytokines displays a novel pathophysiological aspect in itchy skin diseases.

Novel itch mediators: interleukin-31 and autotaxin

More recently, a novel cytokine named IL-31 was shown to have a pivotal role in severe itch and chronic dermatitis, as assessed in mice overexpressing IL-31 [42]. In Nc/Nga mice, IL-31 levels correlated with scratching behaviour [43], which could be ameliorated by the use of anti-IL-31 Ab [44].

In humans, IL-31 levels are increased in itchy skin diseases including chronic urticaria and atopic dermatitis [45•,46]. In atopic dermatitis, levels of IL-31 also correlate with disease severity [45•,46]. IL-31 mRNA has also been shown to be increased in the skin of patients with atopic dermatitis, allergic contact dermatitis and prurigo nodularis [47]. Interestingly, staphylococcal superantigens, which represent a general trigger factor for atopic dermatitis rapidly induced IL-31 mRNA expression in the skin and in peripheral blood mononuclear cells of atopic individuals [47], which may have an impact on itch sensation (Fig. 1). Cellular sources of IL-31 are represented by skin infiltrating CLA+ T-cells, CD4+ T cells and peripheral blood CD45R0 CLA+ T-cells [48]. Another cellular source of IL-31, which has been identified more recently is dermal mast cells [27••].

As IL-31 receptors are not only expressed on epithelial cells including keratinocytes but also on dorsal root ganglia (Fig. 1), IL-31 represents an interesting target for the therapy of itch [47,49].

Recently, autotoxin was identified as a common mediator in different forms of cholestatic pruritus [50••]. Chronic pruritus in cholestatic liver diseases occurs frequently. Kremer *et al.* [50••] showed in their study that lysophosphatitic acid (LPA) and autotaxin (ATX) are significantly increased in serum levels of patients with cholestatic pruritus. Moreover, serum levels correlated with itch intensity in the patients. Further, intradermal injection of LPA into the skin of mice induced scratching behaviour assuming that LPA and ATX play a pivotal role in cholestatic itch possibly serving as a novel target for future therapeutic interventions.

Stepwise approach in the diagnosis of itch

Identifying the cause of patients with chronic itch is a challenge. Before initiating a laboratory investigation or imaging analysis, a careful history of the onset and course of itch, medical history, drug intake *et cetera* should be performed (Table 1). Further, a clinical examination

Table 1 Stepwise graduated diagnostic assessment of patients with chronic pruritus (modified according to the AWMF-German Guidelines)

History	Onset and course of pruritus, presence and onset of skin lesions, known systemic and dermatological diseases and allergies, predisposition for atopic dermatitis, medical history, drug intake, family history
Clinical examination	basic: Physical examination including lymph nodes, skin examination, dermographism in-depth: Internal, neurologic, psychosomatic, gynecologic/urologic consult
Laboratory investigation	basic: Electrolytes, erythrocyte sedimentation rate, blood count, differential blood count, total protein, protein electrophoresis, iron metabolism, blood glucose, uric acid, urea, creatinine, liver transaminases, bilirubin, alcalic phosphatase, hepatitis serology, thyroid function test, total IgE serum level, PSA, urine status, fecal-occult-blood test in-depth: For example: level of folic acid, zinc, vitamin B12, antimitochondrial antibodies, immunoglobins, indirect immunofluorescence, antibodies against thyroid gland, parathyroid hormone level, parathormon, porphyrine, bone marrow investigation
Diagnostic procedures	Skin biopsy (histology, direct immunofluorescence) in case of presence of skin lesions, which could not have been classified upon clinical criteria, and performance of an additional skin biopsy, helicobacter pylori 13C urea breath test, lactose deficiency H2- exhalation test, endoscopy/biopsy
Imaging	basic: Chest radiograph, ultrasound abdomen in-depth: CT-scan or MRI-scan especially for tumor detection and in case of neuropathic pruritus, ultrasound lymph nodes

CT, computed tomography; IgE, immunoglobulin E; PSA, prostate specfic antigen.

including the skin, the lymph nodes and dermographism represent an important part in the diagnostic approach of itch (Table 1). Basic laboratory investigations include blood count, differential blood count, besides billirubin and so on, which can also be investigated in depth including, for example zinc, vitamin B12 (Table 1). Diagnostic procedures include the skin biopsy with subsequent specified analysis including histology and direct immunofluorescence. Last but not least, basic imaging analyses are helpful in the diagnostic approach of chronic itch using the chest radiograph and ultrasound of the abdominal part. In-depth analysis includes the computed tomography scan or MRI scan for example in tumor detection as a cause of itch (Table 1).

Stepwise approach for the therapy of itch

An important factor in itch is dry skin. Thus, a moisturizing therapy should be initiated. A wide array of medications (e.g. β-blockers, allopurinol) and psychogenic factors but also hot spices, alcohol, and hot beverages can intensify the sensation of itch, which should be avoided accordingly and are included in the first step of therapy for itch (Table 2) [51].

Local therapies for the stepwise approach to treat itch

Lesions caused by scratching should be treated with classic dermatological therapies [e.g. emollients, topical corticosteroids, short-term relief with polidocanol, urea, menthol as first step therapy (Table 2)]. The second step of therapy includes the treatment of the cause of itch (Table 2). During the third step of therapy chronic localized lesions from scratching (e.g. lichen simplex, prurigo nodularis) are treated, for example with capsaicin cream [51] (Table 2). Further, calcineurin inhibitors including tacrolimus and pimecrolimus are included in the third step of itch therapy as shown in atopic dermatitis, prurigo, chronic-irritant hand eczema and genital pruritus [52] (Table 2). Topical cannabinoid agonists may also be used for the treatment of itch as shown in patients with atopic dermatitis [53] (Table 2).

Many patients require a combination of systemic and topical therapies due to itch and secondary scratch lesions. Whole-body phototherapies with UV-A or UV-B light are included in the third step of therapy (Table 2) and can be used separately or in combination. UV-therapy can be helpful in patients with contraindications to systemic agents, for example in itch during late-term pregnancy, in the elderly patient and in patients in whom other antipruritic therapies have failed. However, UV-light therapy is not recommended for patients using calcineurin inhibitors.

Systemic application of drugs for the stepwise approach to treat itch

The newer and nonsedating H1-antihistamines are a popular treatment option in chronic pruritus due to their good efficacy, low costs and lowside-effects. They are included in the fist step of therapy of itch (Table 2). In patients with chronic urticaria an updosing of nonsedating antihistamines up to four-fold had been recommended by an international panel of experts as shown in the latest guideline of the European Academy of Allergy and Clinical Immunology [54]. This may also account for other itchy skin diseases. Because modern antihistamines may, at least in higher dosages, also be able to reduce the extent of degranulation and release of other pruritogenic medicators by mast cells, this may further enhance the antipruritic effect of antihistamines [55].

Most other currently employed systemic approaches of treating itch target the central nervous system. For

Table 2 Stepwise approach for the symptomatic treatment of itch

	Therapy
First step	Moisturizing therapy Avoidance of triggering factors Initial symptomatic therapy: Nonsedating H1 antihistamines (sometimes updosing needed) Topical corticosteroids
Second step	Symptomatic therapy according to the cause of itch
Third step	In case of unclear cause and nonresponse during the second step: Symptomatic topical and/or systemic therapy including, for example capsaicin, calcineurininhibitors, cannabinoidagonists, naltrexone, gabapentin, UV-therapy, immunsuppressives (cyclosporine), antidrepressants Clinical studies in special centres
Supporting therapy during each step	Treating the cause (multidisciplinary) Basic therapy In case of sleeping disturbances: sedating H1 antihistamines, tranquilizer, trizyclic antidpressives or neuroleptics Psychosomatic consultation, for example trainings in case of automatic scratching habbits In case of erosive scratching lesions: disincentive therapies (e.g. Lavasept), local administration of steroids

Adapted from [51].

example, in clinical practice, anticonvulsants including gabapentin and pregabalin have been shown to be effective in the treatment of itch that are included in the third step for the therapy of itch [56] (Table 2). The exact mechanism of action for these drugs, however, is not yet clarified.

Another third step therapy include antipruritic drugs including agonists or antagonists of the opioid system (Table 2). Naltrexone, for example is an oral opioid receptor antagonist with a long-lasting, selective blockade of μ-opiate receptors. Naltrexone has been shown to be partially effective in relieving itch in case series and controlled trials of patients with chronic kidney diseases and in various dermatological diseases [57•]. Based on the assumption that opioid-induced itch is mediated by activation of μ-opioid receptors and can be suppressed by activation of κ-opioid receptors, it was thought that κ-agonists may be an effective treatment for itch. This is supported by the finding that the κ-receptor agonist nalfurafine effectively reduced itch in treatment refractory hemodialysis patients [58•].

Various antidepressants have long been used in the treatment of chronic itch and are included in the third step of therapy (Table 2). For example, the antipruritic effectiveness of the selective serotonin reuptake inhibitors paroxetine and sertaline has been documented in controlled studies and case reports of patients with polycythemica vera, somatoform pruritus, paraneoplastic pruritus, and cholestatic pruritus [59].

Mirtazapine, a tetracyclic antidepressant with additional H1 antihistaminic and serotonergic effects has successfully demonstrated an antipruritic effect in idiopathic pruritus, cholestasis, uremia, and neoplasm-induced pruritus [60]. Furthermore, the tricyclic antidepressant doxepin can be used topically and systemically for its additive antihistaminic and anticholinergic effects in pruritus [61].

The exact mechanisms underlying the documented antipruritic effects of the described drugs are not entirely clear. One important aspect, especially for the tricyclic and tetracyclic antidepressants, may be the known antihistaminergic effect of these drugs. Furthermore, central nervous effects of serotonin are thought to have a regulatory action on the itch-related transmission [61].

Experimental and promising treatment strategies

In animal models, the use of anti-IL-31 [44], neurokinin-1-receptor antagonists [62•], and H4-receptor antagonists [63,64] have been proven to be successful for the therapy of itch.

In humans, only a minority of these novel drugs have been evaluated so far in case reports or small case series. In this regard, the neurokinin-1-receptor antagonist aprepitant almost completely controlled severe and treatment refractory itch in three patients with Sézary syndrom [65] and successfully inhibited itch in 20 patients with atopic diathesis, prurigo nodularis and pruritus of systemic origin [66••]. Furthermore, the κ-opiod agonist nalfurafine has been shown to be very effective in a phasis III randomized placebo-controlled trial including 337 patients with hemodialysis-associated pruritus [58•].

Conclusion

Chronic itch is a common problem, which can severely impair the quality of life of affected patients. In the skin and nervous system, complex cellular interactions have a pivotal impact on the pathophysiology of itch. Thus, knowledge of the underlying mechanisms will help us to identify novel treatment strategies, which is displayed by small case series of promising drugs and needs to be further supported by randomized trials.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 499–500).

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