Neuroimmune interactions in allergic skin diseases

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Purpose of review

Recent studies have advanced our understanding that allergic inflammation triggers neuronal dysfunction, thereby modulating inflammation-related changes in affected tissues including the skin. Vice versa, evidence has emerged that inflammatory responses are controlled by neurons. Moreover, structural cells and invading immune cells express neuronal receptors and release mediators which directly communicate with nerve endings in the skin.

Recent findings

During the allergic response, skin cells do not only represent a significant source of neuromediators but also represent targets for neuropeptides or neurotrophins as well as neurotransmitters in the inflamed tissue. During the last decade, it has become obvious that a large variety of molecules influence the adaptive as well as the innate immune response. Beside neuropeptide receptors, proteinase-activated receptors, novel histamine receptors, different cytokine or chemokine receptors play a role in the pathophysiology of atopic and allergic diseases.

Summary

Peripheral sensory and autonomic nerves are critically involved in many pathways of the innate and adoptive immune system during allergic and atopic skin diseases. Further dissection of receptor-mediated and intracellular signal pathways will help to develop more effective therapeutic approaches for allergic and inflammatory skin diseases.

Keywords

allergy, neuroimmunology, neuromediator, proteinase-activated receptor

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Abbreviations

α-MSH	α-melanocyte stimulating hormone
BDNF	brain derived neurotrophic factor
CGRP	calcitonin gene-related peptide
CHS	contact hypersensitivity
NGF	nerve growth factor
PAR	protease-activated receptor
TNF-α	tumor necrosis factor α
TRPV	transient receptor potential vanilloid
VIP	vasoactive intestinal peptide

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Introduction

Understanding the complex pathophysiology of allergic diseases has become a main challenge of clinical and experimental research. Recent evidence indicates that cutaneous allergic and atopic inflammatory processes are influenced by neuronal mediators released directly from neurons or structural cells. In general, allergic diseases of the skin are mediated by the innate and adaptive immune system which, in turn, induces the production of immunoglobulin E (IgE) antibodies (type I hypersensitivity) or T-cell-derived mediators (type IV hypersensitivity). Whether neuromediators play a role in the regulation of immune complex mechanisms (type III hypersensitivity) is unknown.

It has become obvious that neurons and activated structural cells such as keratinocytes, endothelial cells, fibroblasts, epidermal dendritic and Langerhans cells, for example, are capable of releasing neuromediators into the site of inflammation, thereby modulating the immune response. For instance, neurotrophins such as nerve growth factor (NGF) or neurotrophin-4 (NT-4) are well known to mediate inflammatory signals [1•–3•], and show increased levels in patients with atopic dermatitis and psoriasis [4]. Furthermore, the density of neuropeptide-positive nerve fibers is increased in lesions of patients suffering from atopic dermatitis. These results indicate that neurotrophins act on sensory nerves, leading to enhanced nerve sprouting and sensitization. Moreover, enhanced levels of neuropeptides released from nerve endings or resident and immune cells influence the exacerbation of allergic skin diseases such as atopic or allergic contact dermatitis. This review highlights the current concept of a cutaneous neuroimmune network and focuses on recent research projects [1•–3•,5•,6•,7,8•,9] and innovative therapeutic options.

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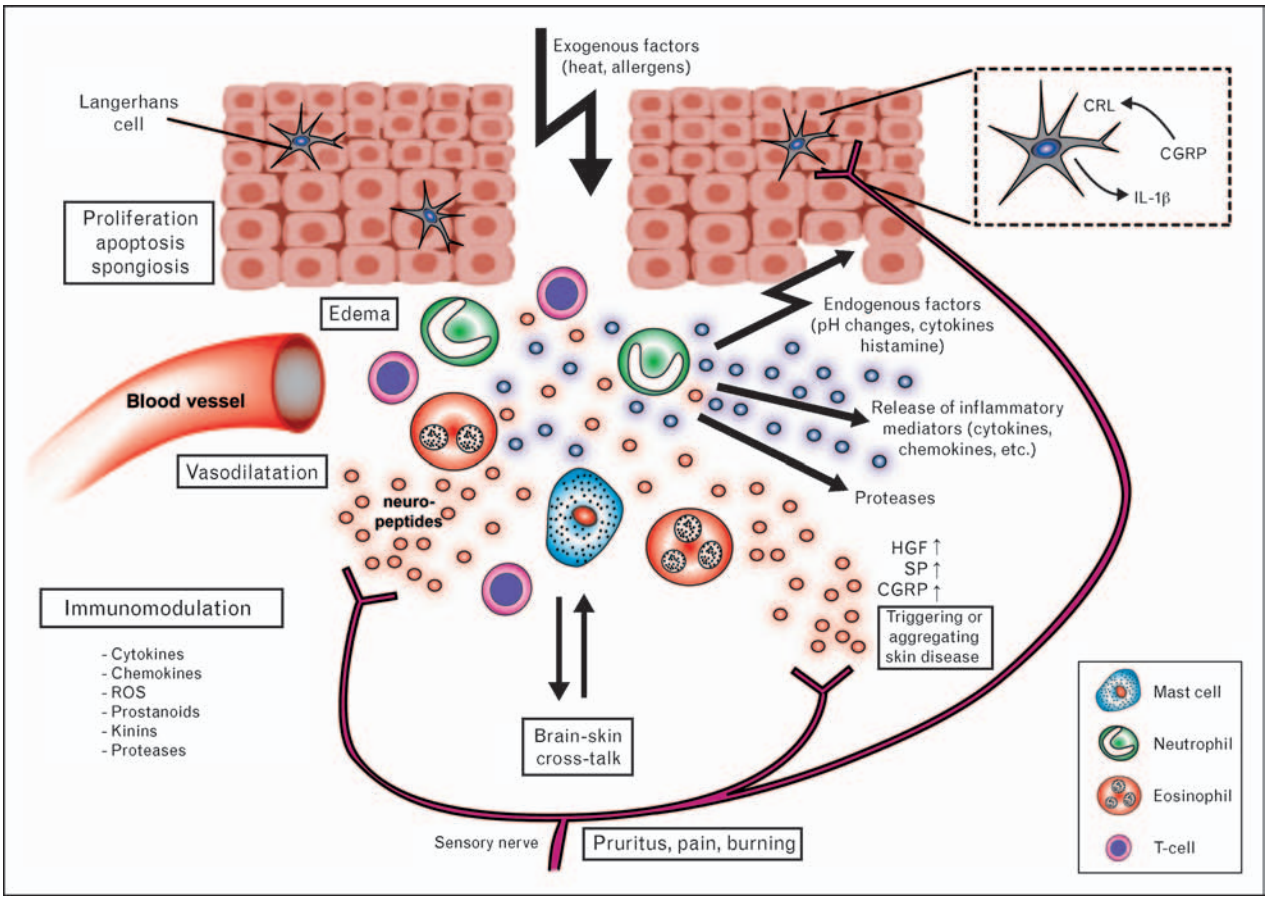
The cutaneous nervous system

The skin is associated with the peripheral nervous system, the autonomous sensory nervous system and the central nervous system (CNS). Innervation of the skin is realized by sensory nerve fibers with an additional complement of autonomic nerve fibers. Unmyelinated C or myelinated Aδ primary afferent nerve fibers transmit sensory stimuli (temperature changes, inflammatory mediators) via dorsal root ganglia and the spinal cord to specific areas of the CNS resulting in nociception, itch, burning or pain. Thus, the communicative network of the skin is carried out by primary afferent sensory nerves [10•]. The modern concept of cutaneous neurogenic inflammation delineates that exogenous (e.g. heat, allergens, haptens, ultraviolet light) or endogenous (pH, cytokines, kinins, histamines, proteases) trigger factors may directly or indirectly stimulate nerve endings from primary afferent neurons. Additionally, a process defined as axon reflex which describes the stimulation of neighboring afferent nerve fibers by peripheral nerve endings leads to the release of neuropeptides [10•], modulating vascular function [11] (vasodilatation, plasma extravasation, endothelial cell activation), immune cell function (e.g. T-cell proliferation, mast cell degranulation, B-cell development), and cell activation (e.g. keratinocyte migration, antigen presentation by dendritic cells) (Fig. 1). The behavioral function of keratinocytes in epidermal immune responses has been recently reviewed in detail [12].

Figure 1 Neuroimmune interactions in allergic skin diseases



Exogenous (irritants, allergens, heat, mechanical, microbiological agents) or endogenous (pH changes, cytokines, kinins, histamine, proteases, neurotransmitters, hormones, 'stress' etc.) trigger factors that may directly (sensory nerve endings) or indirectly (via keratinocytes or endothelial cells) stimulate sensory nerves in the skin. Stimuli are transmitted to the spinal cord and central nervous system. This leads to the recognition of pain, burning or pruritus. In the periphery, nerve endings release neuropeptides [substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) etc.], thereby sensitizing neighboring nerve fibers (axon reflex) or modulate various immune cells (neutrophils, macrophages, antigen-presenting dendritic cells, lymphocytes etc.) in the vasculature or intradermally. This leads to the recruitment of inflammatory cells to the site of inflammation, vasodilatation and plasma extravasation, modulation of immunocyte function (e.g. mediator release from T-lymphocytes, induction of antibodies from B cells, modulation of antigen presentation in Langerhans cells) and regulation of mediator release (cytokines, chemokines, growth factors). The epidermal keratinocytes are also affected by inflammation (proliferation, apoptosis, spongiosis and edema). CRL, calcitonin receptor-like receptor; IL, interleukin; NGF, nerve growth factor; ROS, reactive oxygen species.

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Neuropeptides involved in allergic skin diseases

The so far described neuropeptides consist of a group of small peptides built up by four or more than 40 amino acids. To date, more than 20 neuropeptides have been described and characterized in the skin. These cutaneous neuropeptides predominantly interact specifically with members of a superfamily of G-protein-coupled receptors (GPCRs) with seven transmembrane domains [13]. The common mediators of the immune and nervous system are listed in Table 1. Cells of both systems are able to synthesize and release the mediators and to respond to them via specific receptors. Release of the tachykinin substance P by nerves or epithelial cells affects lymphocyte proliferation, mast cell degranulation and, as recently demonstrated, the migratory behavior of intestinal epithelial cells in rats [14]. Calcitonin gene-related peptide (CGRP) is able to induce vasodilatation, at higher concentrations plasma extravasation, mast cell degranulation and seems to be influenced by female sex hormones [15•].

Studies with female rats demonstrated that β-estradiol potentiates CGRP-induced relaxations in mesenteric and caudal arteries. Besides substance P and CGRP, vasoactive intestinal peptide (VIP) is also localized in both neuronal fibers and cellular elements of the skin. As an antiinflammatory neuropeptide, VIP suppresses the induction of contact hypersensitivity [16], and suppresses macrophage and T-cell function [17••]. Recent research about neuroimmune actions by VIP revealed that VIP significantly reduces the incidence of severe autoimmune diseases such as encephalomyelitis and multiple sclerosis in experimental rodent disease models [18].

Langerhans cells are dendritic antigen-presenting cells in the cutaneous epidermis which are directly associated with CRGP, delineating a functional modulatory role in the cutaneous immune system [19,20]. Most of the studies so far reveal that the neuropeptides such as CGRP are suppressing Langerhans cell function and thus cutaneous inflammation. It has become evident, however, that the suppressive effect of CGRP, for example, depends on certain circumstances such as the maturation status of dendritic cells. The precise conditions with respect to immune adaptation and defense have been described elsewhere [21].

Taken together, neuropeptides participate in pro as well as antiinflammatory neuromodulatory interactions associated with immune and humoral responses. The in-vivo role of pro versus antiinflammatory neuromediators in human allergic reactions, however, is still a matter of debate [10•,22].

Another important factor mediating inflammatory responses between the nervous and the immune system is NGF, essential for nerve fiber development, outgrowth and its maintenance. During inflammation, NGF can be released by keratinocytes, affecting apoptosis and

Table 1 Neuromediators involved in allergic and atopic responses of the skin

Mediator	Receptor	Effects and allergic diseases
CGRP	CGRP receptor on keratinocytes	Vasodilatation, extravasation at higher concentrations. Pain transmission, stimulates TNF-α release from mast cells
Substance P	Neurokinin receptor on sensory nerve fibers, keratinocytes	Extravasation (edema), pruritus, pain burning transmission; release of TNF-α, histamine, prostaglandins from mast cells. Involved in contact dermatitis and atopic dermatitis
NGF	Trk A on mast cells, keratinocytes, fibroblasts and eosinophils	Elevated expression in atopic dermatitis, inflammation. Nerve sprouting. Sensitization of sensory nerves Stimulates the release of tryptase
NT-3, NT-4	Trk C for NT-3 Trk B for NT-4	NT4: upregulated in atopic dermatitis NT3: inhibitory effect in hyperalgesia
IL-31	IL-31R and OSMRβ on keratinocytes, dendritic cells and sensory nerves	IL-31 transcripts in NC/Nga mice and atopic dermatitis. Induces itching Role in neurogenic inflammation?
Kinins	Bradykinin receptors on endothelial cells, immunocytes, keratinocytes, sensory nerve fibres	Bradykinin: modulatory effects on pain perception. Involved in pruritus. Activates TRPV channels
Endovanilloids	TRPV1 on sensory neurons, mast cells, keratinocytes, epidermal and hair follicle cells	Involved in neurogenic inflammation. Antiinflammatory? Itch and pain by short term activation, antipruritic effects (capsaicin) by long term activation
Histamine	Histamine receptor H1R and H4R on sensory nerve fibers, T cells and endothelial cells	Histamine induces itch, plasma extravasation and vasodilatation in certain diseases. Uncertain role in atopic dermatitis. Regulates T-cell function and proliferation
Opiods	μ-, κ-opioid receptor on sensory nerves as well as on keratinocytes	Antipruritic effect of μ-opioid antagonist. Cannabinoids induce release of β-endorphin from keratinocytes. Regulates T-cell and macrophage function. Role in allergic diseases and atopy?
α-MSH	Melanocortin receptors expressed on various skin cells and leukocytes in the skin	Antagonizes IL-1 activity, upregulates IL-10; antiinflammatory peptide

α-MSH, α-melanocyte stimulating hormone; CGRP, calcitonin gene-related peptide; NGF, nerve growth factor; NT, neurotrophin; OSMR, oncostatin M receptor; TNF-α, tumor necrosis factor-α; Trk, tyrosine kinase; TRPV, transient receptor potential vanilloid.

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functions which can be observed during atopic and allergic responses. Additionally, NGF affects mast cell activity and has regulatory influence on skin fibroblast migration and contraction actions of myofibroblasts. Furthermore, NGF has antiproliferative effects when exposed on medulloblastoma cells and induces the overexpression of p73, a putative tumor suppressor gene [23,24]. Other members of the neurotrophin family [NT-3, 4, brain derived neurotrophic factor (BDNF)] are well defined and use a common group of relatively specific high-affinity cell-surface receptors, defined as tyrosine kinase (Trk) receptors. In general, neurotrophins are target-derived neuronal growth factors but have potential roles within the immune system. The influence of neurotrophins has been reviewed recently [25].

Cells of the immune system are able to express both the neurotrophins and their corresponding receptors. Monocytes/macrophages are strong producers of NGF and BDNF in mammals. Exposure to lipopolysaccharide induces the expression of NGF and CGRP in human mononcytes [26]. Moreover, lipopolysaccharide -induced upregulation of NGF controls CGRP expression levels by activating the promoter of the CGRP gene through specific signaling pathways. Since a variety of cells harbor binding sites for CGRPs, NGF may influence skin inflammation by regulating CGRP synthesis in either sensory nerves or immune cells.

Mast cells, the critical effectors of immediate type hypersensitivity, depend on NGF for homing, survival and differentiation. Recently, mast cells were even shown to mediate cutaneous nerve fiber elongation during contact hypersensitivity [27].

Interestingly, release of histamine by mast cells is mediated by α-melanocyte stimulating hormone (α-MSH), melanocortin peptide derived from the common precursor molecule propiomelanocortin, which is known to stimulate melanin production [28]. Several studies [29–31] demonstrate a direct immunoregulatory and antiinflammatory role for this propiomelanocortin-derived peptide in the skin. Immunosuppressive properties attributed to α-MSH are the antagonistic effect on proinflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6 and tumor necrosis factor-α (TNF-α). Additionally, stimulation of cultured fibroblasts with α-MSH resulted in elevated matrix metalloproteinase-1 (MMP-1) expression levels, suggesting that α-MSH is involved in connective tissue remodeling [32].

Transient receptor potential ion channels in neurogenic inflammation

One of the most interesting findings during the last few years was the influence of capsaicin, the active component of chili peppers, on neurogenic inflammation [33]. Capsaicin treatment elicits pain sensation by selectively activating small-diameter C-fibers and triggering cascades of inflammatory events such as release of proinflammatory mediators in skin and mucosa [10•,34,35]. Repeated application of capsaicin leads to desensitization of nerves and thus makes capsaicin suitable for the treatment of inflammatory, painful and pruritic diseases. The molecular target of capsaicin or other vanilloid substances is TRPV1, a vanilloid receptor of transient potential ion channels. Deletion of the responsible gene (VR1) results in the elimination of capsaicin-induced heat sensation [36]. The potential role of TRPV1 in neuropathic and inflammatory pain is supported by several studies indicating that it is upregulated in both diseases [37]. Recently, a protective role could be attributed to TRPV1 in an acute contact dermatitis model [38]. Activation of TRPV1 by prostaglandin E_2 and bradykinin suggests a novel signaling mechanism of pain sensation through promiscuitive activation of an ion channel (responsive to temperature or pH changes) by chemicals such as prostanoids or bradykinin, or by communication with other neuronal receptors [39,40•,41,42]. These effects are mediated, at least in part, by activation of phosphatidylinositol-4,5-bisphosphate and phospholipase C-γ, or protein kinase C-ε [40•].

The finding that TRPV1 channels are also present in a variety of nonneuronal cells like human epidermal and hair follicle keratinocytes, dermal mast cells, dendritic cells and fibroblasts expands our knowledge about the putative role of TRPV1 beyond that of pain perception [43–47]. In addition, TRPV1 ion channels are involved in the cellular processes such as proliferation, differentiation and apoptosis of keratinocytes [44,47]. The observation that NGF is stimulating the promoter activity of rat TRPV1 in PC12 cells supports the hypothesis that NGF is capable of directly inducing the expression of TRPV1 on the transcriptional level and thus influences pivotal signal transduction pathways of inflammation [48•]. The role of the other TRPV ion channels in allergic skin disorders, however, remains to be elucidated.

Communication of cytokines and chemokines with peripheral nerves in atopic and allergic diseases

Cytokines and chemokines are inflammatory mediators and important activators of sensory nerves, thereby contributing to neurogenic inflammation, pain and pruritus. Recent studies reported that the expression of IL-31, a newly discovered cytokine mediating pruritus and atopic-like dermatitis, is elevated [49,50•,51,52]. IL-31, a four-helix bundle cytokine, is primarily expressed by activated T cells skewed toward a T-helper type 2 (T_H2)-type cytokine profile. Elevated expression of IL-31 in mice results in skin dermatitis resembling atopic dermatitis.

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Keratinocytes express both subunits of the receptor for IL-31, IL-31RA and oncostatin M receptor (OSMR), and enhance the expression of chemokines which subsequently induce infiltration of immune cells. Recently, it was demonstrated that dorsal root ganglia are an abundant source of IL-31RA among all the other tissues tested. The assumption is that dorsal root ganglia represent the site of mRNA production for afferent sensory neurons. OSMR, the other essential subunit of IL-31 signaling, is detectable on a subset of nociceptive neurons in dorsal root ganglia projecting to the dermis of the skin. Taken together, T-cell derived IL-31 may induce pruritus by directly modulating sensory neurons.

Other cytokines such as IL-18 may also be involved in skin lesions of atopic dermatitis, psoriasis or allergic contact dermatitis [53]. Recent data indicate keratinocyte-derived IL-18 to be involved in the regulation of sensory nerve function via β-endorphin stimulation (M. Steinhoff, unpublished observation). The biological role of this keratinocyte/nerve interaction in human skin disease, however, has to be determined.

Proteinase-activated receptors in cutaneous allergic and atopic diseases

As recently reviewed [54–56], protease-activated receptors (PARs) can be cleaved and thus activated by a variety of serine proteases involved in inflammatory processes characterized by vasodilatation, extravasation, and regulation of leukocytes. Furthermore, PARs are capable of stimulating the release of neuropeptides such as CGRP and substance P, thereby influencing the neurogenic pathway of inflammation. Naturally occurring agonists from the skin (trypsins, mast cell tryptase, kallikreins) or synthetic agonists of PAR_2 or PAR_1 regulate inflammatory responses by activating proinflammatory mediators such as TNF-α, IL-1, IL-8, macrophage inflammatory protein 1α or CD63, for example. In dorsal root ganglia, PAR_2 is detectable in the majority of rat sensory nerves colocalizing with CGRP and substance P, indicating a direct and possibly autocrine mechanism of PAR_2 activation [34,54,57]. Recent findings suggest a putative role of neuronal PAR_2 in allergic contact dermatitis, atopic dermatitis as well as pruritus [58,59,60•]. Ongoing studies with different knockout mouse strains will hopefully highlight the role of PAR_2 in allergic or atopic diseases and cutaneous barrier dysfunction [61].

Neuroimmune interactions in skin pathophysiology

Atopic dermatitis is a common skin disease characterized by pruritus and eczematous skin lesions accompanied by normal or elevated serum IgE levels against multiple allergens including house dust mites and pollen, for example. One of the most extensively studied substances so far is histamine, which is believed to be one of the key players in the development and reoccurrence of atopic dermatitis. Nonsedative antagonists of histamine-1 receptors, however, are only of limited use for the treatment of this chronic pruritic and inflammatory disease. The recently discovered histamine 4 receptor (H4R) seems to be linked to the pathology of inflammatory skin diseases since pruritus was selectively inhibited by the treatment with a H4R antagonist or in H4R knockout mice [62•]. Furthermore, the assumption arises that the H4R effects may result from actions on periphery neurons. This is in good agreement with the finding that histamine is not the sole mediator of pruritus in atopic dermatitis, and that mediators other than histamine, such as mast cell tryptase by activating PAR_2 on sensory nerves, may be more important for the induction of itch in atopic dermatitis [58]. The final role of tryptase and the H4R as therapeutic targets in atopic or allergic skin diseases, however, awaits further clarification.

One of the most interesting findings of the last decade is that injection of neuropeptides into the skin mimicks the characteristic triple response which is defined as erythema, wheal and flare [63,64]. Substance P is speculated to be a central player and modulator of itch in atopic dermatitis. Recent studies demonstrated that substance P exerts its modulatory effects via tachykinin-1 (NK1) receptor [65]. Inhibition of scratching behavior could be achieved by the application of NK1R antagonists in a picrylchloride-induced dermatitis model in NC/Nga mice. The regulatory influence of substance P affects the expression of cytokines in response to house dust mites (*Dermatophagoides farinae*, Der f). Moreover, substance P enhanced the Der f-induced proliferation of peripheral blood mononuclear cells and led to a marked upregulation of IL-10 mRNA expression profiles while downregulating IL-5 mRNA expression [66]. Another study with HaCaT cells (a human epidermal keratinocyte cell line) and dermal fibroblasts [67] demonstrated that matrine, a phytoalkaloid, inhibits substance P-induced IL-1β, IL-8 and monocyte chemoattractant protein-1 production in HaCaT cells and fibroblasts, while it increases the production of interferon-γ in HaCaT cells.

Moreover, the NC/Nga mouse, an inbred mouse strain and atopic dermatitis animal model, was used to demonstrate the trigger effects of psychological stress during the onset of atopic dermatitis [68••]. For example, pretreatment with corticotropin-releasing factor (CRF) blocked the stress-induced development of atopic dermatitis in these mice. The current assumption is that a central neural pathway for itching may be related to CRF and other opioid peptides, whereas a peripheral pathway is linked to histamine, proteases, prostaglandin E_2, TNF-α, and bradykinin. Other neuropeptides such as β-endorphin and α-MSH possibly influence the pathophysiology of atopic dermatitis in an antiinflam-

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Table 2 Neurodermatology in allergic and atopic skin diseases: future perspectives on research and therapeutic strategies

Mechanism	Possible perspective	Selected reference
Pro or antiinflammatory capacity of neuropeptides	Development of novel antiinflammatory strategies by neuropeptide agonists or antagonists, respectively	[10•,15•]
Role of neurotrophins in inflammation and itch	For example, anti-NGF therapies against allergic or atopic disease. Anti-NT-4 therapy in atopic dermatitis	[70]
Effects of proteases and PAR_s on inflammation and itch	Serine protease inhibitors or antagonists of PAR_2 for treatment of inflammation and itch	[32,57]
Role of IL-31 in inflammation and pruritus	IL-31 receptor antagonists targeting keratinocytes and neurons during cutaneous inflammation	[47,48•,82]
Role of the epidermal barrier in allergic skin diseases	Keratinocyte function and epidermal barrier dysfunction, interaction with neuronal peptides	[10•]
Role of neuronal cytokine receptors in allergy and atopy	Identification of novel neuronal receptors of the cytokine and chemokine family	[82,83]
Role of TRPV1, 3, 4 in allergic and atopic disease	Antiinflammatory and antipruritic treatment using specific TRPV1 agonists such as modified forms of capsaicin or resiniferatoxin. Modulators of TRPV-3, 4 function	[10•,34,84]
Role of antiinflammatory POMC peptides in allergy and atopy	Antiinflammatory therapies by α-MSH agonist, for example	[85]
Role of calcineurin inhibitors in neurogenic inflammation	Neuronal calcineurin pathways as antiinflammatory therapy in neurogenic inflammation	[86]
Role of histamine receptors 3 and 4 in neurogenic inflammation and pruritus	Histamine-3 agonists and histamine-4 receptor antagonists for the treatment of allergic and atopic diseases	[87–89]
Defining intracellular signaling pathways of neuropeptide receptor-mediated modulation of inflammation	Generation of specific neuropeptide receptor modulators or inhibitors of intracellular signaling pathways	[10•]

α-MSH, α-melanocyte stimulating hormone; IL, interleukin; NGF, nerve growth factor; NT-4, neurotrophin-4; PAR, protease-activated receptor; POMC, propiomelanocortin; TRPV, transient receptor potential vanilloid.

matory and antipruritic fashion. Beta-endorphin was detected in keratinocytes clustered around μ-opioid receptor-positive nerves and in unmyelinated nerve fibers. The expression of μ-opioid and κ-opioid receptors was detected at reduced levels in skin biopsies of atopic dermatitis patients due to its internalization in keratinocytes [69]. Interestingly, dry skin induction in mice with deleted cutaneous μ-opioid receptor revealed that these mice scratch less often than their wild type counterparts, indicating an important role in itch sensation and skin homeostasis [70].

Elevated serum levels of neurotrophins such as NGF and BDNF have been reported in atopic dermatitis. The enhanced expression of NGF in mast cells and keratinocytes together with the property of NGF to stimulate histamine release suggests that NGF may regulate mast cell–nerve and keratinocyte–nerve interactions in atopic dermatitis [71]. Interestingly, increased levels of trk B receptors on peripheral blood eosinophils could be detected in patients suffering from atopic dermatitis compared with healthy controls. The functional role of this eosinophil-mediated process on neuroimmune responses in the skin still remains to be clarified [72].

Contact hypersensitivity (CHS) is a type of cutaneous inflammation that is exacerbated by neuropeptides such as substance P [73–75]. Inhibition of substance P leads to a reduced responsiveness of CD at the site of allergen contact. Substance P stimulates mast cells to produce TNF-α and increases the activity of secreted TNF-α, but has no stimulatory effect on the production of IL-3 and IL-6 [76]. The opposite effects are fulfilled by CGRP, which is capable of suppressing TNF-α release from mast cells in UV-light induced systemic immunosuppression [77]. Recent studies suggest that both μ and κ opioids enhance CHS in females in a more intense way than in males [78]. The observed sex differences in CHS immunoreactivity upon opioid treatment may be related to signaling through the NK1 receptor, thus potentiating opioid effects [79•].

Future studies using NK1R antagonists (e.g. spantide II) will have to reveal the usefulness of blocking substance P-mediated effects in allergic and atopic diseases. Hemokinin-1 is a recently identified substance P-related neuropeptide affecting B-cell function [80–82]. Thus, hemokinin-1 may be involved in the regulation of immunoglobulin synthesis during allergic reactions. The role of this novel neuropeptide in allergic and inflammatory diseases, however, is still unknown. Possible future perspectives on research and therapeutic strategies are highlighted in Table 2. [10•,15•,32,34,47,48•,57,70,82–89].

Conclusion

The peripheral sensory and autonomic nervous system modulates the function of the skin during health and disease. As described above, the interaction between structural skin cells with peripheral nerves plays a pivotal role in controlling pro as well as antiinflammatory

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pathways during skin homeostasis and disease. Recent discoveries, such as the revelation of direct protease/neuronal (by tryptase), cytokine/neuronal (e.g. IL-31) pathways or novel neuropeptides [pituitary adenylate cyclase-activating polypeptide (PACAP), hemokinin-1 (HK-1)] indicate a fine-tuned communication between the immune and the nervous system. The molecular mechanisms of the neuromediator-induced modulation of allergic and atopic diseases are still an exciting field of research. Finally, the generation of drugs suppressing proinflammatory or inducing antiinflammatory effects during allergic diseases allow for future innovative strategies.

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