

Neuroimmunological findings in allergic skin diseases

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Purpose of review

Recent studies have gained widespread information about the complex regulation of genetic, environmental, immunologic, and pharmacologic factors that contribute to the development of allergic inflammatory skin diseases such as atopic dermatitis. Neuroimmune mechanisms, however, still remain to be elucidated. This review will focus on the interaction between the cutaneous immune and peripheral nervous system in allergic inflammatory skin such as atopic dermatitis.

Recent findings

Neuropeptides and neuropeptide-positive nerve fibres are prominently increased in lesions of atopic dermatitis. The density of nerve fibres is increased while peripheral nerve endings are in an active state of excitation. In this regard, neurotrophins particularly described for their functional role on nerve cells are also expressed in atopic dermatitis skin. In addition, neurotrophins modulate the functional role of eosinophils as main target effector cells in atopic dermatitis, as described recently. Interestingly, eosinophils are capable of neurotrophin as well as neuropeptide production itself, pointing to a bidirectional communication between neuronal cell populations and main target effector cells.

Summary

Neurotrophins and neuropeptides modulate both the functional activity of sensory neurons and immune cells. We have therefore developed the concept of a neuroimmune network between target effector cells and sensory nerves that links pathogenic events to dysfunctions of the cutaneous immune and peripheral nervous system in allergic inflammatory skin diseases.

Keywords

atopic dermatitis, eosinophils, neuroimmunology, neuropeptides, neurotrophins

Abbreviations

α-MSH	α -melanocyte-stimulating hormone
BDNF	brain-derived neurotrophic factor
CGRP	calcitonin gene-related peptide
NANC	nonadrenergic noncholinergic
NGF	nerve growth factor
NKA	neurokinin A
SP	substance P
VIP	vasoactive intestinal polypeptide

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1528-4050

Introduction

To date, the immunological network in allergic airway inflammation has been well defined. Several lines of evidence suggest a role for neuro-mediators like neurotrophins and neuropeptides in allergic airway inflammation [1[•],2,3]. In the skin, however, there is a lack of information about possible interactions of the cutaneous nerve and immune system. Similar to the bronchial hyperreactivity in allergic airway inflammation, inflammatory skin such as atopic dermatitis is characterized by a cutaneous hyperreactivity to nonspecific stimuli, pointing to neuronal reflex circuits. Pruritic lesions in atopic dermatitis are characterized by an increased density of nerve fibres within the skin [4]. It is likely that the enhanced innervation of lesional skin areas results from the vicious circle of pruritus, scratching, worsening of eczema, with subsequently intensified pruritus. In this regard, neuropeptides as well as neurotrophins, which have been studied particularly in the developing nervous system, are suggested as possible key players in atopic dermatitis, bridging the gap between the peripheral nervous system and immune cells (Fig. 1). This review focuses on the neuroimmune network in allergic inflammatory skin such as atopic dermatitis.

The neuronal network in the skin

The skin is equipped with a dense network of highly specialized afferent sensory and efferent autonomic nerve branches that can be found in all skin layers [5,6]. The afferent somatic nerves derive from dorsal root ganglia with fine unmyelinated (C-) or myelinated (A δ -) fibres. Both types of nerve fibres act as receptors for physiologic stimuli such as physical trauma and low mechanical stimulation. In addition, C-fibres communicate tactile sensation (pain, temperature, itch, and proprioception) to the central nervous system and release neuropeptides into the local milieu. The innervation of

Curr Opin Allergy Clin Immunol 5:419–424. © 2005 Lippincott Williams & Wilkins.

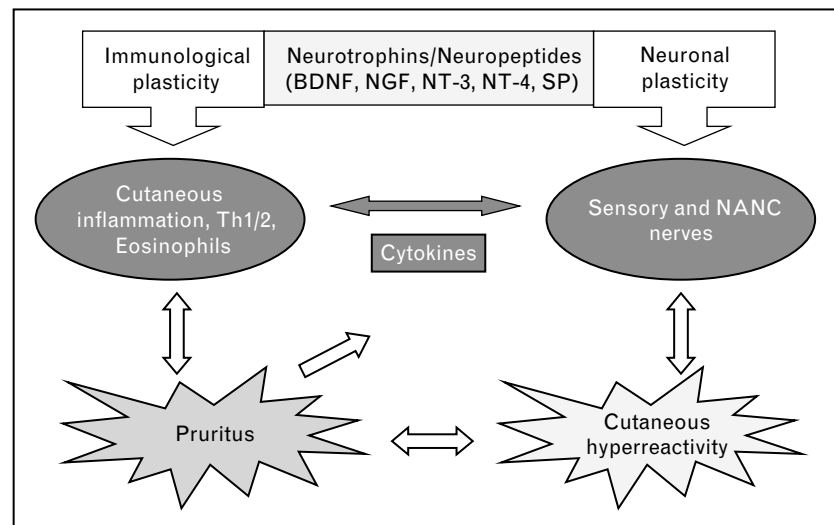
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Current Opinion in Allergy and Clinical Immunology 2005, 5:419–424

Figure 1. Concept of the neuroimmune network in allergic inflammatory skin

Neuropeptides and neurotrophins are bridging the gap between the cutaneous immune and nerve system, as potent mediators for the immunological and neuronal plasticity. BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; NT, neurotrophin; SP, substance P; NANC, nonadrenergic noncholinergic.



the skin can be functionally divided into adrenergic, cholinergic, and nonadrenergic noncholinergic (NANC) neuronal pathways, which are not strictly anatomically separated. Autonomic adrenergic and cholinergic nerves, which release acetylcholine and norepinephrine, represent only a minority of cutaneous fibres innervating eccrine, apocrine, and sebaceous glands, and blood vessels. They activate target cells via muscarinic and catecholaminergic receptors.

The sensory NANC system which is divided into an excitatory (e-NANC) and an inhibitory (i-NANC) part contributes to the afferent system controlling skin function. Neurotransmitters of the e-NANC system are substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP). Mediators of the i-NANC system represent nitric oxide and vasoactive intestinal polypeptide (VIP).

Patients with atopic dermatitis often suffer from severe itch. The transducers of itch are a subpopulation of the receptive endings of unmyelinated slow-conducting fibres of the C-group [7^{••}]. Recently, the downregulation of the epidermal μ -opiate receptor, which is the endogenous ligand for β -endorphin, was assessed in atopic dermatitis [8^{••}], suggesting a histamine-unrelated induction of chronic pruritus. Indeed, the main pruritogenic mediators of atopic dermatitis so far have not been fully investigated. SP represents a potent pruritogenic neuropeptide in atopic dermatitis. In this regard, SP-containing mast cells were found to be increased in a murine model of atopic dermatitis (NC/Nga mice), pointing to a role in itch regulation [9[•]]. Also neuropeptides other than SP are suggested to take part in the itch circle. Phototherapy, well known for its inhibitory effect on itch, downregu-

lates CGRP and SP-positive nerve fibres in atopic dermatitis skin [10,11^{••}]. In addition to neuropeptides, histamine, prostaglandins, serotonin and bradykinins act as pruritogenic factors on C-fibres [6].

The density of nerve fibres in subacute, lichenified and prurigo lesions of atopic dermatitis is higher compared with that seen in uninvolved skin [4]. In addition, the diameter of atopic dermatitis lesional nerve fibres was found to be much larger than in healthy controls, because of the large number of axons in each nerve fibre in atopic dermatitis [12]. Nerves in epidermal layers of atopic dermatitis are described as thin, and barely visible, which run without curving through the epidermis [8^{••}]. A loss of the surrounding sheath of Schwann cells suggests an active state of excitation of the free nerve endings in atopic dermatitis skin lesions [4]. As shown by immunohistology and electron microscopy, hypertrophy of individual nerve fibres and hyperplasia of nerve bundles are frequently observed in dermal atopic dermatitis lesions. Pinocytotic vesicles in the periphery of basal keratinocytes facing nerve endings which contain many neurovesicles suggest reciprocal effects between both cell types. In this regard, it is well known that nerve growth factor (NGF) secreted by basal keratinocytes causes hypertrophy of the peripheral nerve system [13]. In addition, dermal contacts between mast cells and nerves are increased in atopic dermatitis skin compared with that seen in nonatopic controls [14], suggesting the ability to maintain neurogenic inflammation through activation by SP and CGRP. In asthma, localization of eosinophils to nerves is associated with nerve plasticity/remodelling. In this regard, it was recently shown that eosinophil-derived major basic protein 1 (MBP1) regulates nerve plasticity preventing their apoptosis [15^{••}]. The role of eosinophils

in nerve plasticity/remodelling in inflammatory conditions such as atopic dermatitis skin still remains to be elucidated, however.

Psychoneuroimmunological mechanisms in atopic dermatitis

In atopic dermatitis it has been suggested that the hypothalamic–pituitary–adrenal axis might be suppressed in response to mental stress [16]. Psychological stress transiently increases the number of CD8⁺ T lymphocytes and eosinophils in atopic dermatitis, in contrast to healthy controls [17]. In addition, atopic dermatitis patients with high baseline levels of IgE are associated with increased CLA⁺ and CD8⁺ T lymphocytes and T cells expressing Th2 cytokines upon psychological stress [18^{*}]. Emotional stress also has an impact on peripheral neurotrophin and neuropeptide levels. In a study performed by Aloe *et al.* [19] plasma levels of the neurotrophin NGF were significantly increased in men after the emotional stressor of a parachute jump. Moreover, computer-induced stress was described by increased levels of SP and VIP besides an enhancement of allergen specific skin weal response in atopic dermatitis [20]. Emotional stress is therefore suggested as a pivotal modulator for neuroimmune interactions, especially in atopic dermatitis.

Influence of the neuroimmune network by neurohormones

Proopiomelanocortin-derived peptides, originally identified as pituitary neurohormones, are produced by several extra-neural tissues, such as the lung and the skin [21^{**}] (Table 1). In the skin they are produced by melanocytes, keratinocytes, endothelial cells, Langerhans cells, mast cell fibroblasts, monocytes, and macrophages [21^{**}]. In healthy skin these peptides are detectable only in low concentrations in epidermal cells. In contrast, proinflammatory cytokines (IL-1), bacterial endotoxin, but also ultraviolet light are strong inducers of proopiomelanocortin-derived peptide expression. α -Melanocyte-stimulating hormone (α -MSH) represents the best characterized of the eight known proopiomelanocortins. It controls melanogenesis in pigmentary cells and has potent anti-inflammatory, antimicrobial, immunomodulatory actions [2,22]. α -MSH inhibits the production of a number of proinflammatory cytokines including IL-1 β , IL-2, IL-4,

IL-6, IL-13, IFN- γ , and tumour necrosis factor (TNF)- α . In addition, α -MSH inhibits the expression of costimulatory molecules (CD86, CD40, intercellular adhesion molecule 1) on antigen-presenting dendritic cells. Moreover, α -MSH reduces the production of allergen-specific IgE as shown in a murine model of allergic airway inflammation [2]. While downregulating proinflammatory cytokines, α -MSH increases the antiinflammatory cytokine IL-10 and inhibits the activation of transcription factors such as nuclear factor κ B. In the skin, α -MSH inhibits the sensitization and the elicitation phase of contact hypersensitivity reactions as shown in murine models. In addition, α -MSH induces tolerance, underlining its potent role in neuroimmune mechanisms in allergic inflammatory skin.

Tachykinins in the cutaneous network

Tachykinins such as SP, NKA, neurotensin, CGRP and VIP are localized in both neuronal fibres and cellular elements of the skin [23]. They have been described in primary sensory neurons (unmyelinated C-fibres and small myelinated A δ -fibres) and are distributed around eccrine sweat glands and blood vessels. In addition, these neuropeptides are produced by nonneuronal cells such as monocytes, keratinocytes, microvascular endothelial cells, Merkel cells, fibroblasts, T lymphocytes, and eosinophils [24–26]. They are released by a variety of stimuli and have various effects including vasodilatation, submucosal gland secretion, facilitation of cholinergic neurotransmission, stimulation of mast cells, B and T lymphocytes, eosinophils and neutrophils. In the skin, SP, NKA, and CGRP are the main mediators of the weal and flare reaction generated by the axon reflex [27]. Thus, SP, NKA, CGRP, and VIP contribute to the regulation of skin blood flow [28,29] and VIP to the regulation of sweat secretion [30]. Tachykinins mediate their effects via neurokinin receptors. The neurokinin-1 receptor is the high-affinity receptor for SP. NKA binds with high affinity to neurokinin-2, whereas the neurokinin-3 receptor is the ligand for neurokinin B.

Investigation of the skin reactivity to intradermally injected SP, NKA, neurotensin, VIP and CGRP showed a significant reduction of weal and flare response in atopic dermatitis patients but not in controls [31]. This effect

Table 1. Expression of neuro-mediators in atopic dermatitis skin, nerves, peripheral blood and peripheral blood eosinophils

Atopic dermatitis	SP	CGRP	VIP	α -MSH	NGF	BDNF	NT-3	NT-4
Skin	-/+ [34]	+ [32]	+ [32]	+ [21 ^{**}]	+ [50 [*]]	ND	ND	+ [41]
Nerves	+ [14]	+ [14]	- [32]	ND	ND	ND	ND	ND
Peripheral blood	+ [53]	ND	ND	ND	+ [53]	+ [44 [*]]	ND	ND
Peripheral blood eosinophils	ND	ND	ND	ND	+ [56]	+ [44 [*]]	ND	ND

SP, substance P; CGRP, calcitonin gene-related peptide; VIP, vasoactive intestinal peptide; α -MSH, α -melanocyte-stimulating hormone; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT, neurotrophin; ND, no data.

points to a desensitization of afferent nerve endings suggesting a natural tachyphylaxis of the target structures such as mast cells and blood vessels. Indeed, VIP immunoreactivity is markedly increased in atopic dermatitis skin [32] whereas VIP receptor expression on atopic dermatitis mast cells is significantly decreased [33]. In addition, SP levels were described in lower amounts in lesional skin of atopic dermatitis patients compared with controls, whereas SP and CGRP-positive nerve fibres were found to be increased in atopic dermatitis lesional skin [14,32,34] (Table 1).

There is also evidence, as shown by in-vitro studies, that tachykinins can directly affect the functional role of immunomodulatory cells. SP increases the proliferation rate of peripheral blood mononuclear cells of patients with atopic dermatitis compared with controls [35]. In addition, SP activates eosinophils as shown by increased eosinophil-derived neurotoxin and eosinophil peroxidase release, increased superoxide production, and induction of chemotaxis in human airway and equine eosinophils [36–40].

Functional role and cellular sources of neurotrophins in the skin

Several cell types of the human skin are able to produce a variety of growth factors, including NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) [13,41–43]. A close relationship between expression of such mediators and increased innervation has not been established so far. In this regard, however, neurotrophins have recently been shown to be exceptional in supporting survival of neurons in the central and peripheral nervous system.

Neurotrophins have recently gained widespread attention in atopic diseases such as asthma, rhinitis but also in atopic dermatitis. On the one hand they transmit their action via the low-affinity pan-neurotrophin receptor $p75^{NTR}$ belonging to the tumor necrosis factor superfamily to which all neurotrophins bind with similar affinity [44•]. On the other hand, there are the high-affinity neurotrophin receptors of the tyrosine kinase (trk) family to which all neurotrophins bind with high affinity and specificity. NGF binds to trkA, BDNF and (NT-4) to trkB, and (NT-3) to trkC [44•]. Recently, $p75^{NTR}$, trkA-C expression was shown on eosinophils of bronchoalveolar lavage fluids of patients with asthma after segmental allergen provocation [45]. In addition, however, peripheral blood eosinophils of allergic rhinitis patients constitutively express trkA, trkB and trkC receptor [46]. Interestingly, a higher expression profile of $p75^{NTR}$ and trkB receptors on peripheral blood eosinophils of patients with atopic dermatitis compared with nonatopic healthy controls was assessed recently [44•].

NGF represents the best characterized member of the neurotrophin family. It is essential for the survival, development, differentiation and function of peripheral sympathetic and sensory neurons and basal forebrain cholinergic neurons in the central nervous system [47]. NGF also acts as a neurotrophic molecule in the skin. It stimulates the sprouting of nerve fibres and modulates the synthesis and expression of neuropeptides such as SP [48]. In an animal model, NGF was not only able to reverse the decrease of transmitter content caused by capsaicin but also restored the peripheral function of primary afferent neurons [49]. Therefore, NGF is considered to be a primary candidate as a regulatory molecule in neuropeptidergic responses.

Recently, NGF gene expression was found in atopic dermatitis skin [50•] (Table 1). In the skin NGF induces skin fibroblast migration and myofibroblast contraction, whereas fibroblasts themselves produce NGF and express trkA, indicating an important role for NGF in the field of skin wound repair [51]. Whether BDNF, NT-3, and NT-4 also contribute to skin remodelling, however, still has to be elucidated. The close proximity of nerve fibres and capillaries throughout the skin suggests that a mutual regulation may exist between nerve fibres and endothelial cells. Indeed, human dermal microvascular endothelial cells produce NGF, implicating wound repair [52].

Chronic inflammatory prurigo lesions of atopic dermatitis skin are characterized by an increased expression of NT-4 by keratinocytes [41] (Table 1). Interestingly NT-4 production can be induced by IFN- γ injection, which itself is known to have a beneficial effect on pruritus. Also, systemically, neurotrophins are increased in atopic dermatitis, as shown by increased levels of NGF, BDNF, and SP compared with nonatopic controls [44•,53] (Table 1).

Eosinophils constitutively express messenger RNA for NGF and NT-3 and synthesize and store these proteins intracellularly, and continuously replenish them [54,55]. NGF but also BDNF contents are higher in freshly isolated peripheral blood eosinophils of atopic dermatitis patients compared with healthy controls [44•,56] (Table 1). In addition, NGF levels significantly correlate with MBP contents in eosinophils of atopic dermatitis patients [56].

It is well known, that the apoptosis of peripheral blood eosinophils is significantly delayed in eosinophils of atopic dermatitis patients in contrast to those without the condition [57]. Stimulation of eosinophils with NGF and BDNF significantly inhibited the apoptosis of eosinophils [44•,58]. In addition, BDNF also induced the chemotactic activity of peripheral blood eosinophils in

atopic dermatitis, whereas this effect was not shown in healthy controls [44^{*}]. Neurotrophins also exert a direct functional influence on eosinophils by increasing their release of IL-4 after NGF stimulation and eosinophil protein X release after stimulation with BDNF or NT-3 [46]. Accordingly, eosinophils are a source of neurotrophin which may count for the bidirectional pathway on neuro-immune interactions in atopic dermatitis skin. Direct neuronal effects of eosinophil-derived neurotrophin in atopic dermatitis, however, are still under investigation.

Conclusion

In summary, the interaction of the cutaneous immune and peripheral nervous system plays a crucial role in skin homeostasis. Through the widespread expression of neuropeptides and neurotrophins in immune organs and in immunocompetent cells, these molecules are the main candidates for the participation in the complex, interdependent network of mediators that modulate neuronal reflex circuits, skin inflammation, and skin remodelling. It is tempting to speculate that influencing the neuroimmune network will represent a future therapeutic strategy for allergic skin diseases.

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