

Atopic Dermatitis and the Nervous System

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Abstract Due to the narrow associations between the skin, immune system, and nervous system, nerve endings are very important in the pathophysiology of inflammatory dermatoses and especially in atopic dermatitis. Many neurotransmitters and nerve growth factors that are released in blood or skin are involved in neurogenic inflammation, which dramatically enhance the inflammation induced by immune cells. During times of stress, their release is highly enhanced. In atopic dermatitis lesions, there are many specific changes in skin neurobiology and neurophysiology. These interesting data suggest that novel therapeutic possibilities can be imagined.

Keywords Atopic dermatitis · Skin · Nerve · Neuropeptide · Neurotransmitter · Inflammation

Introduction

Atopic dermatitis is an immunological disease in which the activation of immune cells induces eczema. However, these cells are not isolated and the interactions between these cells and both the skin and the nervous system are garnering increasing attention.

The role of the nervous system was first studied after the clinical observations that stress was able to trigger skin

eruptions. This role was sometimes called into question until the 1990s [1] because it was poorly understood. However, new data clearly demonstrate that nerve cells are dramatically involved in the pathophysiology of atopic dermatitis. The term “neurodermitis”, which is often used in German to denote “atopic dermatitis”, appears to be appropriate.

The Neuro–Endocrino–Immuno–Cutaneous System

The skin’s innervation is very dense. Nerve fibers innervate the skin within the hypodermis, dermis, and epidermis up to the outermost epidermal layers. In the skin, neurons can have anatomical contacts with all types of cutaneous cells by way of axon terminals that contain neurosecretory vesicles. These connections could be considered synapses because the intercellular distance is less than 300 nm [2]. Paul Langerhans [3] had suspected such connections with Langerhans cells but it was only recently confirmed that Langerhans cells are in contact with axons via both the cell body [4, 5] and the dendrites [5]. Contacts between nerve fibers and keratinocytes in the epidermis have also been described [6]. In the dermis, contacts between nerve fibers and mast cells [7], as well as contacts between dermal dendritic cells and axons [8], were observed.

Among the various neurotransmitters and neurohormones, approximately 30 have been described in human skin (Table 1) [9, 10]. Most are neuropeptides while some are neurohormones (prolactin, melano-stimulating hormone [MSH], adrenocorticotrophic hormone [ACTH]) or catecholamines, enkephalins, endorphins, or acetylcholine. Nitric oxide (NO) is the simplest and most evolutionarily conserved neurotransmitter in the skin [11].

In the skin, neurotransmitters are synthesized by nerve fibers and Merkel cells [12], as well as Langerhans cells,

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Table 1 Neurotransmitters that are involved in AD pathophysiology

Neuropeptides	Others
ACTH (adrenocorticotrophic hormone)	Acetylcholine
CGRP (calcitonin gene-related peptide)	Angiotensin
CRH (corticotropin-releasing hormone)	DOPA
Endorphins	Dopamine
Enkephalins	Epinephrine
Galanin	Histamine
GRH (gastrin-releasing hormone)	Norepinephrine
MSH	NO
Neurokinin A	Serotonin
Neurokinin B	
Neuropeptide Y	
Neurotensin	
PHI	
PHM	
Prolactin	
PTH (parathyroid hormone)	
Somatostatin	
Substance P	
VIP	

keratinocytes, melanocytes, and all immune cells (granulocytes, lymphocytes, monocytes–macrophages, and especially mast cells). Nonetheless, the presence of neurosecretory granules has been described only in nerve endings and Merkel cells. The mechanisms by which other cells synthesize neurotransmitters remain poorly understood. Most of the cutaneous cells also possess receptors to the neuromediators [13].

Hence, skin cells are able to express neuronal markers and neurotransmitter receptors and have the ability to produce neuromediators as nerve cells. For example, Langerhans cells and their precursors express certain proteins that are usually encountered in cells of the nervous system, i.e., protein S100 and specific neuronal enolase [14, 15]. If they are denervated, these cells are able to express PGP9.5 [16, 17]. Langerhans cells are able to produce pro-opiomelanocortin (precursor to MSH, ACTH, and β -endorphin) [18]. Through cell surface receptors, neuromediators (calcitonin gene-related peptide (CGRP) [4], substance P [19], gastrin-releasing peptide (GRP) [20], and alpha melanocyte-stimulating hormone (α MSH) [21]) have the ability to modulate functions of Langerhans cells, which appear to be central cells linking the skin, immune system, and nervous system [22].

Neuromediators exert effects on cutaneous cells. This activity is typically mediated by receptors coupled to protein G. Neuromediators modulate the functions of all cutaneous cell types: endothelial cells, muscle cells, eccrine

or apocrine glandular cells, immune cells, fibroblasts, and epidermal cells. For example, substance P [19] can inhibit antigen presentation to lymphocytes, through NK1-type receptors on both Langerhans cells and T lymphocytes. CGRP inhibits antigen presentation [4]. Furthermore, incubation with CGRP inhibits the induction of B7-2 in mice [23], seems to limit the production of interleukins 1 and 12 by Langerhans cells, and enhances interleukin-10 production [24]. The inhibitory powers of CGRP have also been found in vivo. The CGRP inhibits contact and delays hypersensitivity reactions by way of local effects [25]. This effect seems to be partly responsible for the immunosuppression induced by exposure to ultraviolet radiations [26]. The effects of neurotransmitters on skin cells are so numerous [27–32] that it is not possible to be exhaustive here.

A system is defined as a group of organs and/or cells that interact and allow a common function. The neuroendocrine system, immune system, and skin share properties and interact in ways that allow a common function. These three systems are often considered to be independent from one another. However, we propose the concept of the neuro–endocrino–immuno–cutaneous system (NEICS) [13] because these three systems are closely linked anatomically and physiologically, as well as during the course of certain diseases. There are physical linkages (such as cellular contacts between nerve fibers, cutaneous, and immune cells), chemical linkages (such as cutaneous secretion of neuromediators and receptors to these neuromediators on cutaneous cells), functional linkages (modulation of cutaneous and/or immune functions by the neuromediators), and interactions between the skin, nervous system, and immunity during the course of illness. All NEICS cells communicate with a common language. The words of this language, i.e., neurotransmitters and cytokines, mediate the maintenance of the homeostasis between the different cell types.

Other actors of the NEICS are neurotrophins: nerve growth factor (NGF), brain-derived nerve factor (BDNF), and neurotrophins 3 and 4 (NT-3 and NT-4). These factors are growth factors for neurons and keratinocytes [33, 34], have anti-apoptotic effects, and are involved in the release of neurotransmitters and control of skin inflammation [35].

The Hypothalamo–Pituitary–Adrenal Axis

The hypothalamo–pituitary–adrenal axis (HPA axis) is defined as the axis characterized by a hierarchy in which the hypothalamus produces corticotropin-releasing hormone (CRH), which induces the release of adrenocorticotrophic hormone (ACTH) by the pituitary gland, which itself induces the release of cortisol by adrenocortical glands. Especially in times of stress, the HPA axis plays a major

role in chronic inflammatory disorders and atopy [36]. Because of the endocrine regulation of skin properties, NEICS is a better term than neuro-immuno-cutaneous system.

Notably, an equivalent of HPA axis has been recently described in the skin [37]. Human skin expresses elements of the HPA axis, including pro-opiomelanocortin, CRH, the CRH receptor-1 (CRH-R1), and key enzymes related to corticosteroid synthesis. Skin cells also synthesize glucocorticoids. Expression of these elements is organized into functional, cell type-specific regulatory loops, which imitate the signaling hierarchy of the HPA axis. Differential, CRH-driven responses of defined cutaneous cell populations reproduce key features of the central HPA axis at the tissue/single cell levels and are activated in case of stress.

NEICS in Atopic Dermatitis

The nervous system plays a significant role in most dermatoses, especially in inflammatory and/or atopic and/or autoimmune disorders, by exerting effects on immune cells through neurotransmitters. Skin innervation undergoes many modifications. The levels of some neurotransmitters fluctuate in both the skin and the blood.

In atopic dermatitis, neurocutaneous alterations are observed. SP⁺, VIP⁺ and CGRP⁺ nerve fiber densities increase [38], while adrenergic innervation decreases and somatostatin-immunoreactive fibers disappear [39]. The distribution of dermal and epidermal cells that are immunoreactive for somatostatin is highly disrupted [40], whereas neuropeptide Y-immunoreactive dendritic cells appear in the epidermis [41]. The cutaneous concentration of substance P decreases while the concentration of vasoactive intestinal peptide (VIP) increases [42]. Blood levels of prolactin [43], substance P or nerve growth factor (NGF) [44] and VIP [45] are enhanced during outbreaks of atopic dermatitis.

Substance P enhances IFN γ and IL-4 release from peripheral blood mononuclear leukocytes [46], as well as TNF α and IL-10 release [47] in atopic patients.

CGRP increases interleukin-13 and HLA-DR expression in circulating cutaneous lymphocyte-associated antigen-positive T cells in patients with atopic dermatitis but not in controls [48]. In these patients, CGRP receptor expression is reduced and CGRP increases the IL-13/IFN γ ratio after culture, suggesting an immunomodulatory role of CGRP that exhibits a Th2 pattern in patients with atopic dermatitis but not in healthy subjects. CGRP is also known to regulate Langerhans cell functions [4, 22].

In patients with atopic dermatitis, the skin levels of acetylcholine are strongly enhanced [49]. In the skin of

patients with atopic dermatitis, expression levels of the alpha subunits 3, 7, 9, and 10 are generally reduced whereas mast cells (but not in healthy skin) show alpha3 and alpha5 subunit immunoreactivity [50]. Differences in the subunit messenger RNA (mRNA) levels between lesional and nonlesional skin were observed for the alpha subunits 3, 9, and 10, with higher levels of alpha3 but lower levels of alpha10 subunit mRNA in lesional areas. No difference in the expression levels of the alpha subunits was found between extrinsic and intrinsic types of atopic dermatitis.

Melatonin is decreased in the serum during outbreaks [51] which may inhibit the development of atopic dermatitis-like skin lesions in NC/Nga mice [52].

The role of beta-endorphin has been discussed. Blood levels have been found to decrease in some studies [51] and increase in others [53]. The kappa-opioid system, but not the micro-opioid system, was shown to be downregulated by immunohistochemistry and RT-PCR in the epidermis of patients [54]. Changes in mu-opiate receptor expression were also found [55].

HPA Axis in Atopic Dermatitis

Because of the wide use of steroids in the treatment of atopic dermatitis, adrenal insufficiency has been observed [56]. However, specific abnormalities seem to be related to the disease itself. Indeed, plasma cortisol levels peaked earlier in atopic patients than in controls, and there was an inverse relationship between the time to peak and the extent of atopic dermatitis, which was independent of treatment, in a study on children [57].

Catecholamines are known to modulate IgE-dependent immunity [58] by potentiating IL-4-induced phenotypic and functional changes through the activation of β 2 receptors. The density of these receptors is decreased on both keratinocytes and lymphocytes from patients with atopic dermatitis [59]. Nonetheless, both cell types show a sixfold increase in their K_D values. Based on these results, a polymorphism in the β 2 adrenoreceptor gene was suspected. No association between a particular polymorphic form of the human beta-2 adrenergic receptor gene and atopy was found initially [60]. More recently, an Ala 119 mutation to Asp119 was discovered to cause increased sensitivity to L-phenylalanine [61]. We found [62] a polymorphism that was found in patients with asthma to be seven times more frequent in intrinsic atopic dermatitis than in extrinsic atopic dermatitis. In atopic dermatitis, abnormalities of the adrenergic system are not limited to receptors. Plasma levels of catecholamines are higher because of abnormalities in synthesis and degradation [63]. Immunoregulation under stressful conditions is inef-

fective in patients with atopic conditions, leading to aberrant immune responses and subsequent exacerbation of the disease [36, 64].

Modifications of Skin Innervation in Atopic Dermatitis

Skin innervation is significantly greater in skin lesions of patients with atopic dermatitis than in uninvolved skin. As visualized using electron microscopy, axons bulging with many mitochondria and reduced number of Schwann cells suggest that these free nerve endings are activated. The presence of many pinocytotic vesicles in keratinocytes facing nerve endings with many neurovesicles suggests reciprocal interactions between nerve endings and epidermal cells [65].

This increased innervation is related to growth factors. NGF and its receptor are more highly expressed in lesions than in healthy skin [66]. NGF levels are higher in lesions and correlate with clinical severity and eosinophil counts [67]. The topical application of high-affinity NGF receptor inhibitors improved dermatitis and decreased the density of nerve fibers in the epidermis [68]. Neurotrophin-4 production by keratinocytes is also increased in lesions and its expression is induced by the injection of interferon- γ [69]. BDNF levels are elevated in plasma and eosinophils from patients and BDNF is chemotactic for eosinophils in these patients. A gene polymorphism has been shown to be frequently present in patients with atopic dermatitis, especially in the intrinsic form [70].

Semaphorin 3A (Sema 3A) is known to be expressed by keratinocytes and to inhibit nerve growth. Its production is decreased in atopic skin [71]. By contrast, Sema3A alleviates skin lesions and scratching behavior in NC/Nga mice, a model of atopic dermatitis [72]. Psoralen-ultraviolet A therapy, which is a treatment for atopic dermatitis, alters epidermal Sema3A and NGF levels and modulates epidermal innervation in atopic dermatitis [73].

Atopic Dermatitis and Skin Neurophysiology

Sensory functions of the skin are modified in patients with atopic dermatitis. The two-point discrimination of itch is significantly better in atopic dermatitis patients than in healthy controls [74]. Acetylcholine elicits pain in healthy subjects, itch in patients with lesions, and a mixture of pain and itch in atopics who have just been freed from eczema [75]. In patients, histamine induces itch associated with burnings as opposed to pure itch in healthy subjects [76]. Skin sensitivity to electric current is decreased in patients with extrinsic atopic dermatitis but not in patients with the intrinsic form. This phenomenon appears to be related to an

impaired skin barrier in patients with the extrinsic form [77]. In contrast to healthy subjects, neuroselective transcutaneous electrical stimulation preferentially evokes itch in atopics [78]. Clinical evaluation revealed hypersensory sensitivity in atopics [79], which is correlated with sleep disorders [80].

Vasomotor disorders (“delayed cholinergic blanch”) [81] and impaired sweating function in atopics [82] are attributable to an abnormal sudomotor axon reflex [82] and an autonomic dysfunction [83], with abnormalities of the sympathetic nervous system [83] and increased vagal modulation [84].

Psychosomatic Consequences and the Role of Stress

The influence of stress and psychological factors on the skin implies that there are chemical factors that translate an emotion or stress into a cutaneous lesion [64, 85]. These factors are probably neurotransmitters and hormones. When a stress is experienced, similar phenomena are described in the nervous system, blood, and skin [86–91]. Stress induces alterations of the NEICS and HPA axis through modifications of blood and skin levels of neurotransmitters and hormones. However, stress does not induce atopic dermatitis or other dermatoses in every person. We propose two possible explanations. First, the occurrence of a cutaneous disorder after a stress could be linked to particular personality profiles and perhaps to particular neurotransmitter profiles in response to stress. Secondly, this occurrence could be linked to genetic and immune backgrounds. We consider the second hypothesis to be more probable than the first.

Some clinical studies have demonstrated the role of stress in atopic diseases. For example, negative life events exacerbate asthma [92]. After an earthquake in Hanshin (Japan), atopic dermatitis was more severe when destructions were more catastrophic [93]. Perceived stress is more intense in people with inflammatory dermatoses than in healthy subjects [94]. There were 43 related studies (in 22 articles), of which 34 evaluated the effect of psychosocial factors on atopic disorders and nine evaluated the effect of atopic disorders on mental health. The major atopic disease assessed in these studies was asthma (90.7%) in combination with allergic rhinitis (4.7%), atopic dermatitis (2.3%), and food allergies (2.3%). The overall meta-analysis [95] exhibited positive association between psychosocial factors and future atopic disorders as well as between atopic disorders and future poor mental health. More notably, the subgroup meta-analysis on healthy and atopic disorder populations showed that psychosocial factors had both etiological and prognostic effects on atopic disorders.

Stress could play an enhanced role in patients with intrinsic atopy with beta-2-adrenergic gene polymorphisms [62]. However, there is no documented association between somatic sensitivity to stress and a particular personality profile [96]. Maternal stress could also modulate immunity through the Th2 profile due to the effects of catecholamines [97].

In atopic adults but not healthy subjects, acute stress enhances eosinophil counts and IgE levels [98]. HPA axis disorders are responsible for a switch to the Th2 and an excessive immune response during times of stress [36]. Stress enhances contact hypersensitivity through the activation of dendritic cells which is mediated by the release of norepinephrine from peripheral nerve fibers [99]. Moreover, stress is known to aggravate inflammation through neurogenic inflammation and mast cell degranulation [85, 100, 101], resulting in impaired skin barrier function [102]. It is especially interesting to note that stress directly induces the release of substance P in the skin, which worsens atopic dermatitis [103].

Therapeutic Perspectives

At the present time, the development of new treatments modulating the NEICS is still limited. Such treatments are more frequently used in the context of pneumology or enterology. The first trials have only just been initiated in the field of dermatology.

In terms of potential treatment options, doxepin is an antidepressant drug with antihistaminic and anticholinergic properties. As a systemic treatment, it is effective in the treatment of pruritus in atopic dermatitis, with a weak effect of erythema [104]. The efficacy of a 5-HT agonist in atopic dermatitis [105] has also been suggested.

Calcineurin inhibitors (cyclosporin, pimecrolimus, and especially tacrolimus) have not only immunological and neuronal effects that could explain their effects in atopic dermatitis; they exert a powerful effect on atopic dermatitis that is sometimes accompanied by a burning sensation, especially after alcohol absorption. Calcineurin inhibitors are able to induce neuropeptide release and mast cell degranulation in the skin [106]. Tacrolimus has been shown to be able to induce initial substance P (SP) release by extracellular calcium influx (explaining the observed side effects) and inhibit SP release induced TRPV1 phosphorylation (explaining the effects on pruritus and perhaps atopic eczema itself) [107].

The use of specific antagonists or agonists of neurotransmitter receptors is suitable. First of them could be used in the treatment of itch [108] or may be CRTH2 antagonists [109].

The role of stress and psychological factors in the worsening of atopic dermatitis suggests that psychological

interventions could be effective [110]. A recent meta-analysis [111] included eight articles published between 1986 and 2006. Eight intervention types were tested: aromatherapy, autogenic training, brief dynamic psychotherapy, cognitive behavioral therapy, dermatological education and cognitive behavioral therapy, habit reversal behavioral therapy, stress management program, and structured educational programs. Although this meta-analysis revealed that psychological interventions had a significant ameliorating effect on eczema severity, itching intensity, and scratching in atopic dermatitis patients, a definite conclusion about their effectiveness seems premature.

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