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Review

Clinical and experimental aspects of cutaneous neurogenic inflammation

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Abstract:
The aim of this paper is to present the state of knowledge on cutaneous neurogenic inflammation.
Peripheral effector functions served by afferent sensory neurons underlie the so-called neurogenic inflammation. The mechanism of cutaneous neurogenic inflammation is connected with the release of neuropeptides from the sensory endings. They also exert a number of functions within the immune system. The activity of neuropeptides in the inflammation of the skin can be observed in the form of erythema, edema, hyperthermia and pruritus. Beside these peptides and their receptors, inflammatory skin response, is regulated by tryptase and proteinase-activated receptor 2 (PAR-2). Capsaicin decreases effects of inflammation-induced sensory neuropeptides, which was used in the treatment of diseases caused by inflammation. The activity of transient receptor potential vanilloid receptor 1 (TRP-V1) is associated with the neurogenic inflammation. In inflammatory processes, the neuro- immuno-cutaneous system undergoes activation, which is responsible for triggering and maintening the inflammatory conditions, both in the healthy skin as well as in the pathological conditions, like psoriasis. Skin exposure to UV radiation influences the neuro-immuno-cutaneous system and causes the release of neuropeptides, thereby eliciting inflammatory response in photodermatosis.
In conclusion, understanding the mechanisms and the factors controlling neurotransmitters and their receptors will lead to the identification of novel therapeutic targets for the treatment of cutaneous diseases e.g. pruritus, psoriasis, alopetia areata.

Key words:
cutaneous neurogenic inflammation, skin, neuropeptides, receptors, capsaicin

Abbreviations: CGRP – calcitonin gene-related peptide, ICAM-1 – intercellular adhesion molecules in epidermis, NKA – neurokinin A, NKB – neurokinin B, PAR-2 – proteinase-activated receptor 2, SP – substance P, TRP – transient receptor potential channel, TRP-V1 – TRP vanilloid receptor 1, UV – ultraviolet light, VCAM-1 – blood vessels vascular cell adhesion molecule, VIP – vasoactive intestinal peptide

Introduction

In 1901, Bayliss described vasodilatation, which occurred after electrostimulation of the sensory dorsal root [55]. This experiment was repeated in order to explain whether the afferent elements of the nervous system also play the effector role in the response of the skin to inflammation [10, 17, 27]. Next, by characterization of polymodal and fine chemosensitive fibres (C and Aδ nociceptors), it was explained in what way the nerves can participate in cutaneous inflammation [68].

In 1927, Lewis showed that thermal, mechanical and chemical damage to the skin, including sting of insects and administration of inflammatory mediators (including histamine and SP) triggered the "triple response". Erythema, which is a result of vasodilata-

tion, appears first at the site of injection then there appears circular edema, while the final stage involves development of a flared rim or edge around the circle [32]. Local erythema is a result of the axon reflex and antidromic sensory nerve stimulation-induced release of vasodilative factors (SP, histamine, purines and calcitonin gene-related peptide – CGRP) [7]. Independent research confirmed the results obtained by Lewis, i.e. substance P (SP) was shown to influence microvasculature mainly *via* neurokinin-1 receptor (NK-1) and to mediate the release of histamine from the mast cells of the skin, which was associated with vasodilatation, formation of edema and the release of pro-inflammatory mediators [55].

Experimental and clinical research on the significance of afferent fibers in the skin were reviewed in several very interesting recent articles [6, 8, 55, 62]. However, many aspects of this subject still require explanation [62, 66].

Functions of afferent nerves in the skin

The skin is innervated by afferent somatic nerves with fine unmyelinated C-type or myelinated Aδ fibers. Both types of fibers respond to physiological stimulations, such as physical stimuli (heat, cold, mechanical distension and UV radiation), including mechanical stimulations of low intensity. Upon stimulation, these fibers are capable of releasing various neuropeptides, e.g.: exposure to UV radiation induces release of inflammatory mediators, which originate from afferent cutaneous sensory nerves. Nociceptive fibers, i.e. those which respond to stimuli causing pain belonging also to types C and Aδ, may be activated by chemical agents and biological factors, such as metabolic products of microorganisms or plants (e.g. of proteinase character). These agents enhance the skin sensitivity to physical and chemical stimuli which activate the skin nervous endings. After stimulation, active neuropeptides are released into the microenvironment. Except for the exogeneous factors, also the endogenous stimuli, such as protons (pH changes), hormones, cytokines, proteinases, kinins, and other mediators are released by various cells involved in inflammatory processes, induced by a pathological stimulation of afferent neurons [57, 66].

Autonomic fibers represent only a minority of cutaneous fibers, however, their neurotransmitters, such as acetylocholine and catecholamines play a defined role in the skin. Autonomic nerves also produce neuropeptides, such as calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neuropeptide Y (NKY). In peripheral tissues, neuropeptides occur in perivascular noradrenergic and cholinergic endings and in free afferent endings of neurons [66]. Neuropeptides are involved in the regulation of sweat glands, vasodilation (thermoregulation, blood flow), immunomodulation and cell trophism [45, 66]. Classic autonomic neurotransmitters may also be produced by nonneuronal cells, such as keratinocytes. Muscarinic and nicotinic acetylcholine receptor expression has been described on keratinocytes and Langerhans cells [26, 66, 71], which indicates a role of autonomic neuromediators in inflammation, epidermal function and hair growth [49, 64, 66, 70, 72]. The important problem of the functional role of mediators and their receptors was addressed in the article of Richardson and Vasko [58] and it was concluded that a substance has a direct stimulatory action on sensory neurons if 1) receptors for the excitatory substance are expressed on sensory neurons, 2) activation of these receptors increases calcium entry presumably by depolarization and/or activating currents in sensory neurons, and 3) exposing isolated sensory neurons to the substance stimulates the release of transmitters.

Participation of sensory nerve endings in cutaneous defense reactions

The inflammatory process called the neurogenic inflammation develops as a result of activation of sensory nerves which secrete neuropeptides in various tissues, including the skin. Neuropeptides secreted in the skin are not only neurotransmitters of the pain and pruritus, but also play the role of the immune and inflammatory mediators [55, 57]. The tachykinins – SP and neurokinin A (NKA, substance K, neurokinin α) are responsible for plasma extravasation while the CGRP and SP elicite vasodilation [57].

The term neurogenic inflammation was used primarily for description of plasma extravasation and vasodilation. Both phenomena constitute the vascular response after electrical, thermal and chemical stimulation of sensory nerves [55, 57]. The axon-reflex hypothesis of neurogenic inflammation suggests that damage to tissues triggers the immediate signal through the sensory nerves to the sensory dorsal root ganglion and the central nervous system (orthodromic

reflex), which transmits the sensation of pain. The signal in the opposite direction (antidromic response) causes direct release of neuropeptides in peripherally innervated tissues. Neuropeptide receptors were found on various immune and non-immune cells. A wide spectrum of target cells responding to SP, CGRP and neuropeptides were described [57]. Both, the neurogenic inflammation and inflammatory response to chemical and thermal damage or to administration of agents irritating the skin are reduced or eliminated by prior capsaicin administration, which indicates the participation of capsaicin-sensitive polimodal nociceptive C fibers in these two processes [42]. Reddening around the site of trauma may be stopped by a prior treatment of the skin with capsaicin, which causes depletion of neuropeptide supply from the sensory nerves. The effect of these peptides on target cells is achieved mainly *via* a paracrine pathway and results in erythema, edema, hyperthermia and pruritus. The mast cells and their products play an important role in the neuronal antidromic response in the skin, because they are anatomically related to the cutaneous nerves. Although the precise role of these cells remains to be determined, it is thought that they may participate in PAR-2-related processes [66], which causes inflammatory response *in vivo* [11]. PAR-2 bound to G-protein occurs on keratinocytes (especially in the stratum granulosum), endothelial cells, hair follicles, in the myoepithelial cells of the sweat glands. In the skin affected by the inflammatory process, PAR-2 receptor was localized on keratinocytes and endothelial cells [64]. Model research concerning the skin inflammation carried out by Seeliger et al. [59] on people and mice showed, that PAR-2 was capable of directly regulating the inflammation of the skin *via* the neurogenic mechanism:

1. Tryptase released from degranulated mast cells cleaves PAR-2 in the sensory nerve endings,
2. Activation of PAR-2 stimulates the release of CGRP and neurokinin – SP and NKA from sensory nerve endings,
3. CGRP interacts with CGRP-1 receptor, which induces arteriolar dilation and hyperemia,
4. SP interacts with NKA-1 receptor on the endothelial cells of postcapillary venules, which induces plasma extravasation; edema is a result of hyperemia and plasma extravasation,
5. SP may stimulate degranulation of mast cells, which is associated with providing a positive feedback,
6. Tryptase degrades CGRP and reduces its effects,
7. CGRP inhibits SP degradation by neutral endopeptidase and enhances SP release,
8. Other mediators from mast cells and other inflammatory cells stimulate the release of vasoactive peptides from sensory nerves [66].

PAR-2 participates in the pruritus in inflammatory diseases of the skin [63]. It is supposed that PAR-2 modulation may contribute to treatment of cutaneous neurogenic inflammation [59] and pruritus [65].

Afferent nerves possess specific receptors for neuropeptides, prostaglandins, histamine, neurotrophins, proteases, vanilloids and cytokines, which indicates that there exists an interactive communication network between the sensory nerves and immune cells during the cutaneous inflammation. The majority of cells possessing receptors for neuropeptides synthesize also peptidases, e.g.: neutral endopeptidase (NEP) or the enzyme, hydrolyzing angiotensin I to angiotensin II (angiotensin converting enzyme, ACE), thereby inhibiting inflammatory stimulation caused by neuropeptides. Similarly, cells synthesizing receptors for such neurotransmitters as acetylcholine and noradrenaline synthesize enzymes that control the effects caused by these molecules. Therefore, a close interaction between neuromediators, target cells and neuropeptide-degrading enzymes is critical for controlling cutaneous neurogenic inflammation [66]. Meggs [38] proposed that a central nervous system may sometimes also participate in the network. Neurogenic switching is a hypothesis for a mechanism by which an inflammatory stimulus at one site can lead to inflammation at a distant site. Neurogenic switching occurs when an efferent signal from the central nervous system causes release of neuropeptides at another site, producing inflammation at the second site without local stimulation.

Receptors for capsaicin in the skin

Capsaicin (a vanilloid alkaloid found in red pepper fruit) administered locally/topically very fast causes the sensation of a burning pain. This is the effect of activation of sensory neurons with a small diameter and release of neurogenic inflammation mediators.

Quadruple amount of capsaicin is necessary to induce neurogenic inflammation in psoriasis in comparison with the control (due to the decreased SP contents in nerve fibers in psoriasis) [21]. The axon reflex caused by capsaicin differs from that caused by SP or histamine. Capsaicin administered topically on the

skin induces release of not only the neurokinins, but also prostaglandins and acetylcholine [72]. Administration of capsaicin in laboratory animals stimulates nerve fibers C or causes antidromic stimulation, which then induces SP and CGRP and elicits response involving vasodilation and extravasation in tissues. Neuropeptides mediate the neurogenic inflammation, because prior treatment of the skin with capsaicin alleviates effects of inflammation. Capsaicin reduces topical and systemic reactions mediated by neuropeptides, such as vasodilation, pruritus and pain [35], and also has an influence on reduction of urticarious reactions [45, 69] and disappearance of psoriasis symptoms [5], while in delayed hypersensitivity, capsaicin increases the reaction [20, 45, 73].

Vasodilation and increase in local blood flow is a reaction consistent with antidromic nerve stimulation and capsaicin activity. It was confirmed that chemical or surgical lesion of sensory innervation under experimental conditions might also increase response to inflammation. These incoherent reports reflect the differences in distribution and biological effects of SP and CGRP activity or unpredicted interactions between SP and CGRP, and other inflammatory mediators in various tissues and species [51].

Capsaicin and other factors connected with neuropeptides may be used as healing agents [4], because a long-term administration of capsaicin is neurotoxic to sensory nerves and causes expiration of inflammatory response, which was used in the treatment of chronic inflammatory diseases [66].

The TRP (transient receptor potential channel) family is a new family of temperature-responsive sensory receptors with six transmembrane domains. Low pH level, which accompanies the inflammatory response, may intensify the response of TRP-V1 (TRP vanilloid receptor 1) to stimulations. TRP-V1 participates in the neurogenic inflammation, but the role of the remaining vanilloid receptor-like proteins VRL-1/TRP-V2, TRP-3 and VRL-2/TRP-4 in the cutaneous inflammation remains to be determined [63, 66].

Sensory neuropeptides and their receptors

Neurokinins* are small peptides consisting of 10 to 13 amino acids [66], whose role is associated mainly with exposure to harmful stimuli. There are five neurokinins in the mammalian nervous tissue, i.e.: substance P, neurokinin A, neurokinin B (NKB, neurokinin β), neuropeptide K and neuropeptide γ [47].

Experimental research on rats revealed, that neurokinin release from sensory nerves might be induced by various stimuli, e.g.: capsaicin, electrostimulation of nerves, low pH, ether, formalin, toluene diisocyanate (TDI), histamine, bradykinin, prostaglandins, leukotrienes and cigarette smoke [29].

SP induces vasodilation and edema in different tissues in various species [26]. In the human skin, SP increases permeability of the blood vessel walls for proteins and is released from sensory nerves, which remain in contact with the cells of vascular endothelium, mast cells, hair follicles and epithelial cells [57]. Free nerve endings containing SP were found in dermis papilla and epidermis of the human fingers. These fibers can be found in Meissner corpuscles; they are in close contact with ducts of sweat glands and blood vessels of the human skin. Nerve fibers containing SP were also found in the skin of cats and rats [42].

SP and CGRP obviously play different, complex roles in the physiology of the immune system [25]. SP receptors occur not only on mast cells, but also on lymphocytes, leukocytes and macrophages. These cells may be stimulated by SP to produce cytokines. Macrophages stimulated by SP generate inflammatory mediators: prostaglandin E_2 (PGE_2), thromboxane B2 and superoxide ion [6]. Activation of mast cells and lymphocytes is associated with interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) release [8]. Since the highest SP immunoreactivity has been observed in the perivascular zone and the stratum papillare [41], the role of SP in the skin is connected with keratinocytes as well as hair follicles, mast cells, fibroblasts and epidermal cells. SP level increased in nerve fibers of epidermis in the skin diseases induced by inflammation [66]. SP regulates intracellular adhesion molecules in epidermis (ICAM-1) and blood vessels vascular cell adhesion molecule (VCAM-1), and the release ICAM-1 and chemokines, e.g.: interleukin-8 (IL-8), and due to that it directly influences interaction between the endothelium and leukocytes [48, 49, 66]. In keratinocytes, SP and NKA stimulate production of the proinflammatory cytokines IL-1α, IL-1β and IL-8 [24, 66]. Substance P also modulates expression of keratinocyte cell adhesion molecule (ICAM-1) [66]. SP is chemotactic for mononuclear and multilobar leukocytes, which indicates a relation-

* The term neurokinin is applied to peptides occurring only in mammals, while the term tachykinins refer to species lower than the mammals, though often the same substances belong to both groups [47].

ship of the neurogenic stimulation and infiltration of the skin by the inflammatory cells [44]. Human keratinocytes *in vitro* bind SP and this is a proof that there is a connection between the activity of neuropeptides and keratinocytes [71].

NKA found in mammalian tissues is chemically related to SP. NKA and SP come from the same precursor [40] and are found in the subpopulation of afferent nerves characterized by the sensitivity to capsaicin (confirmed in several tissues in the rat: in the spinal cord, sensory ganglion and skin, and more precisely in the epidermis and dermis) [12, 72]. NKA expression may be regulated by proinflammatory mediators: IL-1, lipopolysaccharides (LPS) [29] and neurotrofins (NGF) what induces vascular response and pruritus, and stimulates the release of TNF [66], histamine, prostaglandins and leukotriene B4 from the mast cells of the skin [18, 66].

Neurokinins bind to their specific receptors: NK-1, NK-2 and NK-3. SP is a ligand of the NK-1 receptor, NKA of the NK-2 receptor and NKB of the NK-3 receptor. In addition each of them interacts with every type of neurokinin receptor [47]. The receptors of NK-1 were found on Langerhans cells, mast cells and keratinocytes [57], papilla of dermis, sweat glands and hair follicles [37]. In the human skin, neurokinins (especially SP) stimulate fibroblast proliferation activated *via* NK-1 receptor. Other studies have reported that sensory neuropeptides are capable of activating keratinocyte proliferation. SP stimulates endothelial cell proliferation. Due to these activities, sensory neuropeptides may contribute to various proliferative skin diseases. This has been confirmed by research on the human skin concerning e.g.: psoriasis and cheloma [37]. SP displays modulating activity by various target cells, since SP receptors were found both in the skin attacked by psoriasis and in the skin that has not been affected by the disease [46]. Other receptors were also demonstrated to be functionally expressed on keratinocytes, Langerhans cells, Merkel cells, mast cells, fibroblasts and epithelial cells [66]. This is a proof of a close relationship between these cells and the epidermal nerves. Understanding of activity of neurokinin receptors and their potential selective antagonists and agonists may help determine and define the role of neurokinins in proliferative skin diseases, which in consequence may contribute to their treatment [7, 66].

Neuropeptides have a long phylogenetic history and are produced only in the nerve cell bodies without a local synthesis in the nerve endings. Numerous neuropeptides are encoded by a single continuous fragment of mRNA, which is translated into one protein precursor. These precursors, as other proteins, are synthesized in endoplasmic reticulum, then transported to the Golgi apparatus, where they are processed. When they leave this apparatus, they are transported to the nerve endings by a fast axon transport [62]. The majority of these endings are situated around blood vessels of the skin, sweat glands, hair follicles and in free nerve endings in epidermis (nociceptive afferent nerve fibers, including the fine myelinated Aδ fibers and unmyelinated C fibers) [37, 45, 62] in the stratum papillare [45] and nerve bundles deep in the skin [37]. Neuropeptides are present not only in skin nerve fibers, but also in skin cells, including: keratinocytes, microvascular endothelial cells, Merkel cells, fibroblasts, Langerhans cells and leukocytes, eosinophils, mast cells, mononuclear cells and neutrophilic granulocytes [34, 53, 62, 66].

In the skin, there are more than 20 other neuropeptides that have been identified in various species [66]. Epidermal growth factor (EGF) is related with the development of psoriasis [41], and other neuropeptides recognized in the skin include: somatostatin, β-endorphin, enkephalin, galanin, dynorphin, atrial natriuretic peptide, melanotropic hormone (MSH), corticotropin releasing hormone and urocortin [66].

SP, NKA and CGRP are found in epidermis and dermis whereas VIP only in dermis [62]. High level of SP, NKA and CGRP was confirmed in the skin of the toes (in the sole), their intermediate level was observed in the skin of the neck, in the front part of the wrist and on the face. The lowest level of SP, NKA and CGRP was found in the skin of the groin, arm, thigh, which is justified by a low sensitivity of these places to touch. The fact that the highest level of SP and CGRP was found in the skin most sensitive to touch is associated with the role of these two neuropeptides as sensory neurotransmitters [14].

Research carried out by Wallengren et al. [72] shows that SP, NKA and CGRP are released from sensory nerve fibers in the human skin in response to physical or chemical factors, e.g.: production of neuropeptides in the skin is increased by IL-1 or UV rays [31]. SP and CGRP release after exposure to UV radiation is significant, because they both have influence on the function of the skin cells during the neurogenic inflammation. SP and CGRP also affect the production of cytokines and chemokins, cell proliferation and cellular adhesion molecule [57].

We may distinguish neuropeptides, which show activity typical of hormones (adrenocorticotropin, prolactin, somatostatin), neurotransmitters (adrenaline, acetylcholine) and peptides, whose activity is connected with the nervous system. Neuropeptides are molecules mediating between the nerve endings, immune system and skin [41] and which play a significant role in the regulation of inflammatory response [58].

Research carried out by Kiss et al. [30] shows that neuropeptides can directly modulate the IL-8/IL-8RA system of keratinocytes and fibroblasts. The increased expression of IL-8RA on keratinocytes by SP and CGRP and elevated production of IL-8 and IL-8RA on fibroblasts by the α-melanotropic hormone (α-MSH) plays a significant role in the inflammatory conditions of the skin [30]. The role of intracutaneous regulation and neuropeptide system, such as SP, in inflammation and restoring of tissues is determined not only by synthesis and secretion of neuropeptides, but also by interaction with receptors on target cells and SP degradation by peptidases such as NEP [2].

By activation of certain neuropeptides, stress may induce degranulation of mast cells thereby modulating neurogenic cutanous inflammation and pruritus. Neuropeptides are capable of activating endothelial cells of small vessels in dermis in humans, as demonstrated by *in vivo* and *in vitro* experiments [66].

The network of neurotransmitters including neuropeptide receptors as well as proteinases play an important role in maintenance of cell cohesion in healthy skin and during inflammatory and immune reactions in the skin [36].

The role of neuropeptides in skin disturbances and their therapy

One of important topics that emerged recently in the area of skin diseases is a proposal that neurogenic inflammation is involved in the pathogenesis of chemical hypersensitivity syndrome [3].

Any disorder mediated by neurogenic inflammation can potentially be exacerbated by environmental chemicals. Study of the hypothesis that chemical hypersensitivity syndromes may result from neurogenic inflammation arising from stimulation of irritant receptors by environmental chemicals may lead to an understanding of this disorders. Neurogenic inflammation as a pathway distinct from antigen-driven, immune-mediated inflammation may play a pivotal role in understanding a broad class of environmental health problems resulting from chemical exposures [39].

The sensory neuropeptides may induce or alleviate the urticarious disease symptoms, hypersensitivity reactions and acne rosacea [66], may influence pathophysiology of the pruritus, psoriasis, atopic inflammation of the skin [52, 66], alopecia areata, acquired vitiligo, nodular prurigo and cheloma [52] and play a significant role in the wound healing process [66].

In 1991, Eedy et al. [13] observed an increased level of SP and VIP in patients with psoriasis. In the same year, Anand et al. [1] confirmed the increased level of VIP in psoriasis, but in their research, SP was not different from the control. Gliński et al. [21] observed an increased VIP concentration in psoriasis, but also a decreased level of SP in this disease. Chan et al. [9] observed an increase in SP in the nerve fibers in patients suffering from psoriasis in comparison with the control. No significant differences were revealed in the contents of VIP and CGRP in the skin affected by psoriasis and lichen planus or seborrheic cutaneous inflammation. However, in five patients with psoriasis, the level of CGRP and VIP level was increased, which was not observed in the control group.

The skin affected by acquired vitiligo contains the increased CGRP levels [33].

An increased number of mast cells and depletion of immunocompetent cells was observed in atopic dermatitis (AD). Neuropeptides may contribute also to changes in thermoregulation, disturbances of sweat secretion, pruritus. First symptom, like sweating and scratching may initiate eczema by the release of neuropeptides from sensory fibers [19]. Fantini et al. [16] indicated the participation of SP in the pathogenesis of AD and showed a significant decrease in SP concentration in the skin affected by the disease in comparison with the healthy skin. However, Toyoda et al. [70] observed an increase in SP in AD. The increase in SP and CGRP in AD and nummular eczema was noted by Järvikallio et al. [28], however, the amount of VIP in their research in both diseases exhibited little difference in comparison with the control.

NK-1 receptor of SP plays a significant role in allergic contact dermatitis (ACD) [58], which together with the activity of CGRP may play an important role in the pathogenesis of ACD [22]. In an allergic contact dermatitis in mice, a reduced level of SP was confirmed [15].

SP and CGRP have been found to be enhanced in urticaria [66]. The increased concentration of SP in the skin affected by the disease was confirmed in pa-

tients with pemphigoid, eczema, phototoxic and photoallergic reactions and burns [14, 45].

The results described above prove that SP, VIP and CGRP play a significant role as modulators of neurogenic inflammation in the pathogenesis of cutaneous inflammatory diseases.

UV skin irradiation causing the release of cytokines, neuropeptides – SP, CGRP and hormones may initiate and maintain an inflammatory response in acute photodermatosis. Some of these mediators also suppress the inflammatory response in the skin to UV rays [57]. CGRP has immunosuppressive properties, while SP and NKA set off the effects of cutaneous neurogenic inflammation [56, 57, 67]. Skin exposure to UV radiation may modulate production of cytokines, chemokins, neuropeptides and neurotrophins and other inflammatory mediators in the skin, which proves that there is also in this condition a close relationship between the immunological, nervous and neuroendocrine systems [57].

Conclusion

In the present work, we discussed the role of nerves in mediating cutaneous inflammation. Information from recent findings established a modern concept of cutaneous neurobiology which stressed that the influences from the central and peripheral nervous system, the endocrine and immune system, and almost all skin cells are interconnected in their functional role in the skin. In these immodulatory mechanisms are involved i.a. neuropeptides. The discoveries concerning the molecular mechanism of action of neuropeptides, especially those explaining the role of their receptors, greatly contribute to better understanding of interaction of skin, nerves and immune system during the neurogenic inflammation process.

Thanks to this knowledge, it is possible to determine new ways of treatment of cutaneous inflammatory diseases associated with the neuroendocrine system.

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