

Cutaneous sensory nerves: mediators of phototherapeutic effects?

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1. ABSTRACT

Exposures to ultraviolet radiation (UVR) during accidental or voluntary sun exposure or treatment with phototherapy or photochemotherapy have a significant impact on the skin. Many skin diseases such as psoriasis, atopic dermatitis, or cutaneous T-cell lymphoma significantly improve by photo(chemo)therapy, though the mechanisms behind the therapeutic effects of photo(chemo)therapy are still far from understood. Various pathways and means through which the energy of UVR from natural or artificial sources is ultimately transformed into biologic effects within the skin have been suggested and cutaneous sensory nerves, neuropeptides, neurotrophins, and certain nerve-related receptors have been among them. In fact a three-dimensional network of sensory nerve fibers derived from dorsal root ganglia intersperses all layers of the skin including the epidermis. In this forefront of defense against environmental impacts (including UVR) on the skin, sensory nerve fibers become targets by itself and closely contact resident and infiltrating cutaneous cells. Thus, terminals of cutaneous sensory nerve fibers, and neuropeptides within these fibers, are in a central position to participate in mediating therapeutic effects of photo(chemo)therapy.

2. INTRODUCTION

Exposures to ultraviolet radiation (UVR) during accidental or voluntary sun exposure or treatment with phototherapy or photochemotherapy have a significant impact on the skin. While some skin diseases such as cutaneous lupus erythematosus worsen after sun exposure there is a considerable number of skin diseases, which significantly improve or even disappear through solar or artificial UVR exposure. Among the UVR responsive skin diseases are conditions such as psoriasis, atopic dermatitis, various forms of eczema, vitiligo, lichen planus, parapsoriasis, mycosis fungoides, and prurigo, to name a few. The pathways through which exposure to the sun or artificial UVR sources affect physiologic or pathologic skin conditions and improve skin diseases have been the focus of research in the field of photodermatology during the last years. Various pathways through which the energy of UVR from natural or artificial sources is ultimately transformed into biologic effects within the skin and beyond have since been described and some of them are the topics of reviews within this special issue of Frontiers in Bioscience.

Scientific work on UVR effects within the skin has mainly focused on resident or infiltrating cells within

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the skin such as keratinocytes, melanocytes, lymphocytes, eosinophils, and mast cells, as well as on cell-derived soluble factors released into the interstitial compartment and eventually into the circulation. Often neglected structures in the description of skin anatomy, histology, physiology, or pathophysiology (including molecular mechanisms upon exposure to UVR) are the nerves within the skin, which will be the focus of this review.

In fact, within the skin there is a dense network of cutaneous nerves which transfer autonomic impulses to the skin and sensory nerve impulses from the skin to the central nervous system. As an integral part of the skin the cutaneous nervous system contributes to the homeostasis of the skin and participates in physiologic and pathologic skin conditions. Within the skin the network of sensory nerve fibers play a particular role in conveying environmental signals from the surface of the skin to underlying skin compartments and, thus, may be of great importance in mediating the therapeutic effects of phototherapy and/or photochemotherapy.

3. ANATOMY OF THE CUTANEOUS SENSORY NERVES

There is a dense three-dimensional network of cutaneous sensory nerves that innervate all parts of the skin including the most upper parts of the dermis as well as the epidermis. The cutaneous sensory nerves originate from ganglion cells located within the cranial and paravertebral ganglia. While the central axons of these ganglion cells project to the dorsal horn of the spinal cord via the dorsal roots, the peripheral axons project to the skin via cranial and spinal nerves. The endings of these nerves finally reach the most upper parts of the skin, where they form a horizontal nervous plexus within the papillary dermis just beneath the dermal-epidermal junction. From this horizontal sensory nervous plexus fine nerves vertically project into the epidermis. On their way the sensory nerves lose their myelin sheets as they penetrate the basal membrane of the dermal-epidermal junction. Thus, within the epidermis we only find unmyelinated nerve fibers, which branch to various degrees and spread within the intercellular spaces between keratinocytes. Some nerve fibers may grow up to the surface of the skin until they reach the border between the granular layer and the stratum corneum, which they do not penetrate. Branching of intra-epidermal nerve fibers (IENF) can be manifold and appear at different heights of the epidermis (1). In the end, epidermal innervation also results in a dense three dimensional network of unmyelinated sensory nerve fibers within the epidermis; a fact that is often neglected since hematoxyline/eosin staining of tissue sections do not show these nerves. It requires special staining e.g. with antibodies against the pan-neuronal marker protein-gene product (PGP) 9.5 to visualize these nerves between the cellular layers of the epidermis. As IENF within the intercellular space branch and grow up to the surface they get in close contact with resident cells within the epidermis such as keratinocytes, Langerhans cells, and melanocytes. They may even get in contact with cells infiltrating the epidermis such as lymphocytes, neutrophils, and

eosinophils. This proximity of IENF to the cellular elements as well as to the stratum corneum of the epidermis might play a major role in the interaction of these elements in physiologic as well as pathologic conditions. The superficial location of sensory nerves in the skin appears to be of utmost importance for their possible role and that of peptidergic soluble factors (i.e. neuropeptides) in mediating effects of UVR. UVR of the shorter (UV-B, 290-320 nm) and longer (UV-A, 320-400 nm) wavebands are capable of penetrating the epidermis or the upper dermis, respectively, thus reaching the most peripheral elements of the cutaneous neurosensory system. At this location, sensory intra- and sub-epidermal nerve fibers become therefore direct targets of UVR. Through the release of neuropeptides they might be capable of mediating, or at least participate in mediating, many physiologic and/or pathologic UVR effects in the skin.

4. PHYSIOLOGY OF THE CUTANEOUS SENSORY NERVES

The orthodromic pathway of sensory nerve impulse processing is characterized by trafficking sensory signals via sensory nerves, dorsal root ganglia, the dorsal root and horn of the spinal cord, the tractus spinothalamicus, and the thalamus to the sensory cortex of the brain. However, peripheral sensory nerves are not only capable of trafficking sensory impulses ortho-dromically but also of trafficking nervous impulses anti-dromically via branches of the peripheral sensory nerves (2). Via anti-dromic impulse trafficking, a chemical or nociceptive stimulus can cause a flare reaction (i.e. erythema) in the surroundings of the site of nervous stimulation without the participation of the central nervous system. In this so-called axon reflex model the flare reaction is part of the "neurogenic inflammation" (2) in which mediators released from sensory nerves induce vasodilation and plasma protein extravasation leading to local reddening, wheal formation, and a surrounding flare reaction. First described by Nicholas Jancso (3,4) using electrical stimulation and chemical irritants such as capsaicin, the pungent ingredient of hot chili peppers which specifically stimulates a subset of unmyelinated C-fibers and thinly myelinated A-delta sensory nerve fibers, this concept of neurogenic inflammation may be of significant importance for a variety of stimuli impinging on the skin. Classical mediators of neurogenic inflammation are the neuropeptides substance P (SP) as well as its co-localized partner calcitonin gene-related peptide (CGRP). However, a variety of other neuropeptides and mediators of the cutaneous neurosensory system as well as mast cell mediators play a role in the neurogenic inflammatory process, which not only comprises local skin inflammation but also interaction with the innate and adaptive immune system (5-8).

5. EFFECTS OF UVR ON THE CUTANEOUS NEUROSENSORY SYSTEM

Most of the work investigating the effects of UVR on cutaneous sensory nerves was done in animal models using single high doses of UVR exposure. Gillardon *et al* (9) were the first to show that inflammatory

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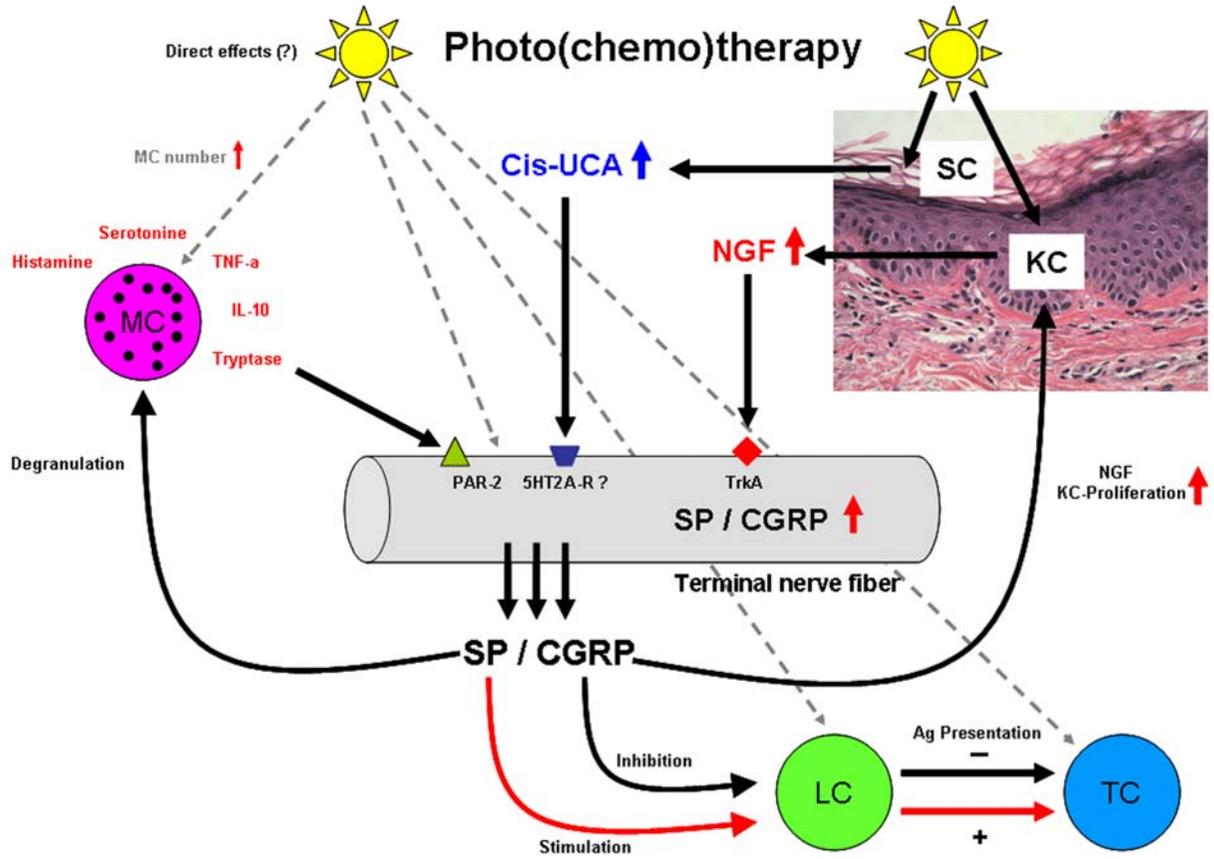


Figure 1. Participation of sensory nerves and neuropeptides in the induction of a cascade eventually mediating the effects of photo(chemo)therapy in the skin. The cutaneous sensory nerves and the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) as a common means for UVR-induced cis-urocainic acid (Cis-UCA), nerve growth factor (NGF) and mast cell (MC) derived mediators to transform the energy of UVR into phototherapeutic effects. See text for further details. SC: stratum corneum; KC: keratinocytes; LC: Langerhans cell; TC: T-cell; TrkA: tyrosine kinase A receptor; 5-HT2A: 5-hydroxytryptamine 2A receptor; PAR-2: protease activated receptor-2; Ag: Antigen

doses of short wave UVR (mostly UVB) were capable of inducing the releasing of neuropeptides such as SP and CGRP from rat skin, leading to a transient reduction of neuropeptide content in the skin 6 h after UVR exposure. In a study by Benrath *et al* (10) pretreatment of rats with SP- and/or CGRP-receptor antagonists before acute high dose UVR exposure reduced the severity of sunburn reaction, also indicating the release of SP and CGRP by UVR. The transient reduction of the neuropeptide content in rat skin, however, was followed by an increase in CGRP skin levels 48 to 72 h after UVR exposure (9). The effect was confirmed also in newborn rats in which Seike *et al* (11) found increased CGRP skin contents 24 to 48 h after high dose UVR exposure. Increased neuropeptide synthesis in dorsal root ganglia (DRG) cells and transport to the peripheral nerve terminals appear to be responsible for the high dose UVR-induced increase of neuropeptides in the skin; a phenomenon also described for other inflammatory models such as arthritis (12).

Nerve growth factor (NGF) appears to play the major role in mediating the increase of neuropeptides in synthesis within DRGs and transport to the site of

inflammation (12). In the arthritis model, increased amounts of NGF released at the site of inflammation reach the DRG cell bodies via retrograde transport along sensory nerve fibers and stimulate mRNA expression and neuropeptide synthesis in DRG cells (12). In a previous study by Gillardon *et al* (13), acute high dose UVR reduced the expression of CGRP mRNA 48 h after exposure when the cutaneous sunburn reaction was at its maximum. This appears to be in contrast to later findings of the same group of authors that observed increased CGRP levels within the skin 48 to 72 h after a high dose of UVR (9). However, a peak of mRNA expression in DRGs early after high dose UVR exposure of the skin and a rapid transcription into the neuropeptide CGRP, which is then transported to the periphery, could be an explanation for low mRNA levels in DRGs and high CGRP levels in the skin 48 h after high dose UVR exposure of the skin.

After exposure to acute high dose UVR the production of NGF transiently increases within keratinocytes *in vivo* in the skin of rats (9) and mice (14). However, NGF may not only increase neuropeptide synthesis and transport from DRG cells to the periphery,

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but also induce the release of neuropeptides such as SP and CGRP (14,15). SP, on the other hand, can also augment NGF production in murine as well as human keratinocytes via the stimulation of high affinity SP receptors, the neurokinin 1 receptors (16). Thus, there is a positive feedback loop between NGF and neuropeptides to further stimulate UVR-induced cutaneous inflammation, i.e. the sunburn reaction.

Beside NGF, urocanic acid (UCA) is implicated to be another important factor in mediating effects of UVR in the skin. UCA is derived from histidine and is present in its trans-isoform within the stratum corneum of the epidermis. Upon UVR exposure trans-UCA undergoes isomerization into cis-UCA (15). cis-UCA has been suggested to play an important role in mediating UVR-induced systemic immunosuppression (17), a phenomenon that is dependent on the presence of mast cells within the UVR-exposed skin (15). However, cis-UCA is not capable of directly stimulating mast cells to release their immunosuppressive mediators such as TNF-alpha and histamine (17). In the search of how cis-UCA induces mast cell degranulation and systemic immunosuppression after UVR exposure, Khalil *et al* (17) have shown that superfusion of suction blister bases at the rat hind footpad by cis-UCA, but not trans-UCA, at concentrations that can be measured in the skin after UVR exposure, caused an increase in microvascular blood flow as detected by an attached laser Doppler-flowmeter probe. The concomitant superfusion of cis-UCA with SP and CGRP receptor antagonists, as well as the impairment of the cutaneous neurosensory system by pretreatment of rats with subcutaneous capsaicin at their 2nd day of life, abolished the increase in microvascular flow induced by cis-UCA superfusion. This indicates that cis-UCA via the stimulation of sensory nerve fibers can trigger the release of SP and CGRP, which then possibly induces the degranulation of mast cells and the eventual release of mast cell mediators. The mechanism, however, by which cis-UCA induces the release of neuropeptides and the possibly receptors for cis-UCA on nerve fibers mediating this release are not yet clear (17). Walterscheid *et al* (18) recently reported that cis-UCA is capable of binding to the serotonin (5-hydroxytryptamin) 2A (5-HT_{2A}) receptors and observed that both UVR- and 5-HT-induced immunosuppression was blocked by either pretreatment of mice with anti-serotonin antibodies or 5-HT_{2A} receptor antagonists. This indicates that cis-UCA derived from the conversion of trans-UCA by UVR exposure mediates its immunosuppressive effects via activation of 5-HT_{2A} receptors. Whether this is also true for the cis-UCA-induced stimulation of sensory nerves and the eventual release of neuropeptides remains to be determined. However, there is evidence that 5-HT_{2A} receptors are located on peripheral sensory nerve fibers (19).

Garssen *et al* (20) showed that UV-induced systemic immunosuppression is dependent on an intact cutaneous neurosensory system and especially on the release of the neuropeptide CGRP. Impairment of the neurosensory nervous system by capsaicin pretreatment of mice early in life prevented UV-induced systemic

immunosuppression. Similarly, pretreatment of mice with the CGRP-receptor antagonist CGRP₈₋₃₇ also abrogated UVR-induced systemic immunosuppression (20). Both UVR- and cis-UCA-induced systemic immunosuppression appear to be dependent on the release of neuropeptides, since the suppression of contact hypersensitivity (CHS) induced by the systemic application of cis-UCA before sensitization to haptens was also abolished in mice pretreated with capsaicin early in life that depleted their sensory nerves of neuropeptides (17). Thus, cis-UCA-induced neuropeptide release could be one of the mechanisms of mediating UVR-induced systemic immunosuppression.

Similarly, NGF was suggested to mediate the systemic immunosuppressive effects of UVR on CHS reactions. As aforementioned, acute UVR exposure induces transient production of NGF by keratinocytes and systemic immunosuppression of CHS (14). A link between the two phenomena was shown in mice, in which systemic suppression of CHS was similarly inhibited by UVR exposure as well as by the systemic application of NGF (14). In this study, UVR-induced systemic immunosuppression was prevented by systemic administration of anti-NGF before UVR exposure, and NGF-induced systemic immunosuppression was abrogated in mice with capsaicin-impaired neurosensory system. These findings suggest that, similar to cis-UCA, UVR-induced NGF stimulates neuropeptide release from sensory nerve fibers. The neuropeptides, such as SP and CGRP, then possibly induce mast cell degranulation and the release of mediators such as histamine, which mediate, at least in part, systemic immunosuppression via stimulated prostaglandin synthesis in keratinocytes and possibly other skin cells (15,21).

Beside in systemic immunosuppression the release of CGRP is also involved in UVR-induced local immunosuppression at least in the CHS model, as shown by Gillardon *et al* (9), who found reduced local immunosuppression in rats pretreated with CGRP₈₋₃₇ before UVR exposure. Direct as well as indirect effects of CGRP on antigen presenting cells within the epidermis, i.e. the Langerhans cells (LC), might play a role for the latter effect. Indeed, CGRP-containing epidermal nerve fibers get into close contact with LC and CGRP has been detected on LC in the epidermis (22). Importantly, UVR exposure as well as local application of CGRP to the skin similarly reduces the number of LC within the epidermis (23), an important step in mediating UVR-induced local immunosuppression. CGRP is also capable of directly inhibiting the antigen-presenting capability of LC *in vitro* via stimulation of cyclic AMP (24) and interleukin (IL)-10 production eventually down-regulating co-stimulatory molecules such as B7-2 (25) and inhibiting antigen-presentation by LC (6). In addition, CGRP inhibits the function of LC via inhibiting the NFkappaB pathway, which appears to play a significant role in stimulating antigen presentation (26).

UVR-induced CGRP might also indirectly affect LC in UV-induced local immunosuppression via the release

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of preformed mediators such as TNF- α through mast cell degranulation. UVR- and CGRP-induced local immunosuppression were both impaired in mast cell deficient mice as well as in mice pretreated with an antibody against TNF- α indicating that TNF- α plays a role in suppressing local CHS by CGRP or UVR exposure (23). This further suggests that UV-induced CGRP release causes mast cells to degranulate and release preformed mediators such as TNF- α , which then mediates local immunosuppression. However, TNF- α may not play an important role in UV-induced systemic immunosuppression as experiments with blockade of TNF- α as well as studies in knockout mice lacking TNF or TNF receptor did not reveal an impaired capacity of UVR to induce systemic immunosuppression (27). However, mast cell degranulation by UVR exposure also causes the release of IL-10, which is involved in the development of tolerance after UVR exposure as well as intradermal CGRP injection (28). On the other hand hapten-specific tolerance is also promoted by CGRP via an IL-10 independent way (29).

6. NEUROPEPTIDE/NEUTOTROPHIN RECEPTORS

Beside the importance of mediators released by UVR via direct or indirect mechanisms it is equally important that these mediators find their receptors on specific target cells to mediate the stimulus induced by UVR. Thus, an UVR-induced alteration of the expression of receptors for neuropeptides and neurotrophins on target cells as well as the expression of receptors for other (inflammatory) mediators on cutaneous nerve fibers might greatly influence the immediate and/or delayed responses to UVR exposure. The CGRP receptor comprises two receptor parts, the calcitonin-like receptor (CLR) part and a receptor activity modifying protein (RAMP). While the receptor for CGRP shares the same CLR with the receptor for adrenomedullin, their RAMP is different; RAMP-1 determines the CGRP receptor while RAMP-2/3 defines the receptor for adrenomedullin (30). The neurokinin 1 (NK1) receptor is the high affinity receptor for SP and is expressed on keratinocytes, endothelial cells, mast cells, as well as on other resident and infiltrating cells within the skin (5). NK1 receptors mediate the stimuli induced by SP during acute inflammation including that of sunburn (10,31). To the best of our knowledge, there are no prospective studies specifically addressing the effects of acute or repeated UVR exposure on the expression of CGRP- or NK1-receptors in the skin. A reason for the lack of studies on CGRP receptors is that until recently (30) there were no reliable antibodies against CGRP receptors available for immunohistochemical investigation. Decreased binding of SP on endothelial cells upon UVA irradiation was demonstrated in patients with atopic dermatitis, in whom the number of SP-positive nerve fibers around blood vessels was increased (32). The expression of NK1 receptors in photoaged skin has been found to be reduced compared to skin protected from chronic sun exposure (33). Whether acute high dose UVR (with mainly UVB) is capable of up- or down-regulating NK1 receptors remains to be determined. However, it would be not surprising, if acute high dose UVR exposure up-regulated

NK1 receptors, thus, boosting proinflammatory signaling during sunburn reaction, while repeated or chronic subinflammatory UVR exposure down-regulated NK1 expression, one of the mechanisms by which repeated UVR exposure during photo(chemo)therapy could reduce inflammation, e.g. within psoriatic plaques. In psoriatic plaques both the content of SP and the presence of NK1 receptors are increased (34,35). One explanation for these apparently contradictory findings is that UVR exposure may increase or decrease NK1 receptor expression, merely depending on the dose and frequency of UVR.

An important regulatory component in the neurotrophin-neuropeptide cascade is the expression of NGF and its high affinity tyrosin kinase receptor A (TrkA). In murine *in vitro* (36) and *in vivo* (14) studies, exposure to acute high dose UVR has been shown to stimulate the synthesis of NGF in keratinocytes. Also, repeated subinflammatory UVR exposures of hairless mice increase NGF immunoreactivity within the epidermis (Sepic and Legat, unpublished observation). In addition, chronic UVR exposed human skin shows increased levels of NGF (33). This is consistent with findings in chronic inflammatory diseases such as psoriasis, in which keratinocytes express increased amounts of NGF (37,38).

UVR exposure also affects the expression of the high affinity receptor for NGF, TrkA. Acute high dose UVR exposure with 3 minimal erythema doses (MEDs) significantly reduced the TrkA immunoreactivity (IR) within the epidermis of normal human skin from 4 to 48 h post-UV (39). Reduced expression of TrkA receptors were also found in non-lesional and lesional psoriatic skin compared to normal skin of non-psoriatic controls. Thus, it appears that there is an inverse correlation between NGF and TrkA expression in the epidermis in normal and inflamed skin. In a study with repeated subinflammatory UVR exposures of mice for 12 weeks there was a significant reduction of TrkA-IR in the UVR-exposed epidermis, while NGF-IR was increased (Sepic and Legat, unpublished observation). Whether these findings play a role for the therapeutic effects of chronic UVR exposure during photo(chemo)therapy of patients with hyperproliferative diseases such as psoriasis has yet to be determined. However, that the interaction of NGF with its high affinity receptor TrkA and alterations of these factors play a role in the expression of key findings of psoriasis such as keratinocyte proliferation, angiogenesis and T-cell activation, is suggested by the finding that K252a, an inhibitor of the high affinity receptor TrkA reduced the clinical signs of psoriasis in a SCID human-mouse xenotransplantation model (40). In addition, Raychaudhuri *et al* reported that in a model investigating the Koebner phenomenon, which describes the induction of psoriatic lesions after traumatizing the skin, NGF levels significantly increased after tape-stripping in uninvolved skin of patients with psoriasis (41). They could also show that the increase of NGF and the proliferation of keratinocytes are early events in this phenomenon preceding the invasion of T-lymphocytes into the epidermis.

A significant UVR-induced increase was also reported for the protease activated receptor-2 (PAR-2) (42).

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PAR-2 is expressed on keratinocytes and melanocytes (43), playing a role in pigmentation and tanning (42). However, PAR-2 is also expressed on sensory nerve fibers, capable of mediating protease-induced neurogenic inflammation (44). Upon activation of PAR-2 on sensory nerves by proteases such as mast cell tryptase the neuropeptides SP and CGRP are released and eventually induce neurogenic inflammation at the site of mast cell degranulation (44).

7. NEUROPEPTIDE DEGRADING ENZYMES

Beside the release of mediators and the type and number of receptors expressed after UVR exposure, the concentration of mediators at the effector site is crucial for the biologic outcome. Mediator concentration, however, does not only depend on the amount of mediator release but also its elimination. The breakdown of neuropeptides by specific endopeptidases such as neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE), thus, is an important determinant for the concentration of neuropeptides at their target receptors. Both, NEP and ACE are located on vascular endothelial cells, fibroblasts and keratinocytes (5) and are capable of degrading SP as well as the SP-inducing peptide bradykinin (BK). NEP knockout mice have an increased baseline plasma extravasation from postcapillary venules, which can be reversed by reconstitution of mice with recombinant NEP or treatment with NK1- and BK2-receptor blockers, which indicates the importance of NEP in degrading substance P as well as BK. Alterations in the expression of these enzymes have also been shown to play a role in inflammatory responses including sunburn reaction, wound healing as well as acute contact dermatitis (ACD) (45,46). NEP knockout mice show significantly increased ear swelling responses 16 to 144 h after high dose UVR (45). In mice pretreated with NEP- or ACE-inhibitors, antigen sensitization is boosted in ACD models and hapten-specific tolerance is reversed (46). These effects are probably mediated by SP acting on NK1 receptors in DC to activate NF-kappaB, which is an important factor for maturation and activation of DC (47). Thus, via the effect on NF-kappaB, SP may have an immune stimulatory effect in acute contact dermatitis, while other neuropeptides such as CGRP, via blockage of the NF-kappaB pathway, may lead to inhibition of antigen presentation by these cells (26).

Exposure to UVR inversely regulates the expression of ACE and NEP (46). In keratinocytes and other cells, UVR exposure down-regulates ACE while it significantly up-regulates the expression of NEP (46). In addition, SP is capable of temporally down-regulating expression and activity of NEP. This suggests that acute UVR, via the release of neuropeptides such as SP, initiates neurogenic inflammation and SP augments and prolongs its own action at the NK1 receptors via temporal inhibition of NEP activity. Whether acute UVR exposure can also increase the expression of NK1 receptors is not yet known. However, in chronically photoaged skin NK1 receptor expression is decreased compared to intrinsically aged skin (33). Thus, increased NEP and a reduction in the number of NK1 receptors may work together in dampening the acute inflammation and modulate the regeneration of damaged tissues.

In photo(chemo)therapy (with low subinflammatory UVR doses) down-regulation of a substance P-driven neurogenic inflammation via the induction of NEP and reduction in the number of NK1 receptors eventually may contribute to reduced proliferation of keratinocytes and eventual clearance of psoriatic skin lesions. Thus, while acute high dose UVR, via the release of cytokines and neuropeptides such as substance P, temporarily reduces NEP expression boosting the acute inflammatory response, repeated chronic UVR exposure during photo(chemo)therapy may increase NEP expression ultimately resulting in clearance of inflammatory skin conditions, such as psoriasis (46)

8. SKIN NERVES AND PHOTO(CHEMO)THERAPY

The mechanisms behind the therapeutic effects of UVR in photo(chemo)therapy are still far from understood (for review see 48) and the potential participation of cutaneous nerves even less so. Both photo(chemo)therapy-induced immune suppression and apoptosis (of keratinocytes and/or immune cells in the skin) alone or in combination may be responsible for the therapeutic efficacy. So far the research in photoimmunology was mainly focused on cutaneous cells and cell-derived mediators when it was sought to understand mechanisms of how UVR actually mediates its effects within the skin after its exposure (18,49-51). Cutaneous nerves and neuropeptides from these nerves, however, were mostly neglected in these considerations. The few studies that investigated UVR effects on cutaneous nerves, as aforementioned, mainly used murine models and single high dose acute UVR in their experimental protocols. However, there are also human studies investigating the participation of neuropeptides and cutaneous nerves in the acute UVR effects, i.e. the sunburn reaction. Benrath *et al* (10) reported about the role of neuropeptides in the later phase of the sunburn reaction. Topical pretreatment of the skin with capsaicin for 4 consecutive days reduced the increase in UVR-induced skin blood flow as well as the decrease in heat pain threshold during this late phase of sunburn reaction, but not within the first 24 h. This suggests a role of neuropeptides in the late but not in the early phase of the sunburn reaction to high dose UVR in humans.

In clinical photo(chemo)therapy, however, not single high doses but rather repeated suberythematous (i.e. subinflammatory) doses of UVR are administered to treat patients with skin diseases such as psoriasis or atopic dermatitis. In a murine study, Garssen *et al* (20) showed that 4 repeated daily UVR exposures with suberythematous doses were capable of inducing systemic immunosuppression of the CHS reaction to a locally applied hapten. In this study, UVR-induced systemic immunosuppression was dependent on an intact cutaneous sensory nervous system and the release of CGRP. Capsaicin-pretreatment early in life as well as pretreated with the CGRP receptor antagonist CGRP₈₋₃₇ abrogated systemic immunosuppression by UVR exposures (20). In one of our own studies (52) repeated treatment of hairless mice with subinflammatory UVR exposures three times per

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week for 4 weeks (a regimen mimicking a clinical phototherapy) increased the number of CGRP-immunoreactive (IR) IENF as well as the content of CGRP in UVR-exposed skin (52). The number of SP-positive IENF also significantly increased. In addition, this treatment regimen induced local immunosuppression of CHS to dinitrofluorobenzene (DNFB) that could be reversed by intravenous pretreatment of mice with the CGRP-antagonist CGRP₈₋₃₇ before sensitization to DNFB. In this study, the total number of PGP 9.5-immunoreactive IENF did not significantly raise in UVR-exposed skin. However, in a second study with UVR treatment periods of more than 4 weeks, beside an increase of CGRP-IR IENF-number, we also observed a significant increase in the total number of PGP 9.5 positive IENF in UVR-exposed skin (Sepic G. and Legat FJ, unpublished observation). That the increase in the number of intraepidermal CGRP-positive nerve fibers as well as the local immunosuppressive effect of repeated UVR exposure in hairless mice was a specific effect of UVR was shown in mice by topical pretreatment with a broadband sunscreen on their back skin before each UVR exposure. In the sunscreen-pretreated mice both the increase in CGRP-positive IENF and the local suppression of CHS reaction by UVR were abrogated (52). The findings of Garssen *et al* (20) and ours indicate that repeated UVR exposure is indeed capable of increasing the content of neuropeptides in the skin exposed to UVR, and, at least in mice, it also causes local as well as systemic immunosuppression.

In a study with human volunteers, daily UVR-exposures with suberythematous UVB doses given over 5 days did increase the amount of extractable CGRP in UVR-exposed skin but not in unirradiated skin (53). In previous studies, repeated exposures to long-wave or solar simulated UVR as well as psoralen plus UVA (PUVA) photochemotherapy also increased the number of skin nerves (54,55). Wallengren and Sundler (56) investigated the number of cutaneous nerves immunoreactive for PGP 9.5, CGRP, and the capsaicin receptor, vanilloid receptor (VR) 1 at uninvolved, i.e. non-lesional, skin sites in 10 patients undergoing photo(chemo)therapy with UVA/UVB, narrowband UVB, or PUVA for various skin conditions such as psoriasis, atopic dermatitis, and nummular eczema. In contrary to the aforementioned other studies, they did not find an increase, but a mean decrease of PGP 9.5-immunoreactive nerve fibers within the epidermis 48 h after the last of 15 to 22 UVR exposures. While CGRP-IR nerve fibers were hardly found in the epidermis of both unirradiated and UVR-exposed skin, they also found a decrease in CGRP-immunoreactive nerve fibers in the dermis of UVR exposed skin (56). VR1-immunoreactive nerve fibers were not affected. The authors suggested that the reduction in the number of cutaneous nerve fibers may provide an explanation how UV treatment may reduce the severity of itching in patients with pruritus. The results obtained by Wallengren and Sundler (56) contradict the aforementioned animal and human studies reporting an increase of neuropeptide content or overall number of skin nerve fibers after repeated UVR. However, the heterogeneity of patients (atopic dermatitis, nummular eczema, psoriasis) and photo(chemo)therapeutic regimens

(UVA/UVB, narrowband UVB, PUVA) in a single small study of only 10 patients could possibly account for these contradictory results. Indeed, the sampling of patients appears to be of great importance for the study outcome since the skin of patients with different skin diseases such as psoriasis, atopic dermatitis, or prurigo nodularis, may have different levels of neuropeptides, neuropeptide receptors, and neurotrophins even without UVR exposure. For instance, a difference in the expression of neuropeptide- as well as neurotrophin-receptors has even been shown in patients with psoriasis depending upon whether they had pruritus or not (35). In addition, it has long been suspected that (psychological) stress may change the level of neuropeptides in the skin of diseases such as psoriasis or atopic dermatitis (57).

It is well-known that skin lesions of patients with psoriasis or atopic dermatitis undergoing photo(chemo)therapy only improve or clear on UVR-exposed body sites but not on sites shielded during UV treatment (58,59). This indicates that local, possibly immunosuppressive, effects of UVR may play an important role in the therapeutic response, and as aforementioned, neuropeptides such as CGRP derived from sensory nerves within the skin may play a role in mediating it. However, systemic mechanisms appear nevertheless to be involved in mediating certain phototherapeutic effects such as the reduction of the severity of itching in patients with pruritus. In a half-body design Gilchrest *et al* (60) investigated the effect of repeated subinflammatory UVB exposures using a half-side UVB-treatment regimen on the relief of pruritus in patients with renal insufficiency. The repeated UVR exposure of one body half not only led to the relief of pruritus on the skin of the exposed body half, but also induced relieve of pruritus on the contra-lateral UVR-shielded body half (60). This clinical study did not investigate the number of nerves in the exposed and unexposed skin, nor did it investigate the possible mediators of this systemic effect of UVR, however, it is conceivable that skin derived factors may have mediated the systemic anti-pruritic effect of half-side UVR exposure. Whether skin nerve-derived neuropeptides were directly or indirectly involved or soluble mediators from cutaneous cells mediated this effect via peripheral or central mechanisms remains to be determined.

9. CUTANEOUS NERVES AND PHOTOAGING:

Cutaneous sensory nerves and their neuropeptides, however, may not only be involved in mediating therapeutic effects of photo(chemo)therapy but possibly also adverse effects upon chronic long-term treatment. Toyoda *et al* (61) found a strong correlation between the number of IENF and the number of photodamaged keratinocytes when comparing pre-auricular (i.e. chronically UVR-exposed) skin and post-auricular (i.e. photoprotected) skin from 20 Caucasian women in their 6th and 7th decade. In addition, increased numbers of sensory nerve fibers have been found in the epidermis and papillary dermis of chronic sun-exposed skin (e.g. forearm) compared to that usually shielded from the sun (e.g. the dorsal aspect of the upper arm) (33). There was also an

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increase in the tissue levels of the neuropeptides SP and CGRP as well as that of the neurotrophin NGF in chronically sun-exposed skin, while the expression of NK1 receptors was reduced, possibly resulting from a direct UVR effect on NK1 receptors and/or a receptor down-regulation due to increased agonist concentrations. The continuing increase in neuropeptidergic and neurotrophic mediators in chronically UVR-exposed skin may possibly result in a continuous state of local immunosuppression, which may allow the survival and further proliferation of epidermal cells, such as keratinocytes and melanocytes, which carry UVR-induced DNA damage and would otherwise undergo apoptosis. The protective effect of NGF and CGRP against UVB-induced apoptosis of keratinocytes and melanocytes via the induction of anti-apoptotic Bcl-2 has previously been shown (62,63). This may thereby promote carcinogenesis in skin chronically exposed to sun, artificial UVR, or PUVA (64) and participate in the phenomenon of photoaging (65).

10. SUMMARY AND PERSPECTIVES

The network of cutaneous sensory nerves has a distinct location in the forefront of defense against environmental impacts on the skin. Due to the proximity of nerve terminals to all components of the skin they have great potential of interacting with resident cutaneous cells as well as with cells infiltrating the skin in response to inflammatory or allergic stimuli. We suggest that local as well as systemic effects by repeated UVR exposure during photo(chemo)therapy are mediated, at least in part, via the direct or indirect involvement of the network of cutaneous sensory nerve fibers and their containing mediators such as neuropeptides, leading to immunosuppression and possibly also apoptosis of keratinocytes and immune cells. However, it is also likely that cutaneous sensory nerves not only play a role in mediating the beneficial effects but also harmful acute (i.e. sunburn) as well as chronic (i.e. photoaging and photocarcinogenesis) adverse events of photo(chemo)therapy. Better understanding of the role of cutaneous sensory nerve fibers and their mediators induced upon photo(chemo)therapy may open the avenue to improve the safety of and/or substitute photo(chemo)therapy by newly designed medications, using disclosed pathways.

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Abbreviations: ACD: Acute contact dermatitis; ACE: angiotensin converting enzyme; BK: bradykinin, CGRP: Calcitonin gene-related peptide; CHS: contact hypersensitivity; CLR: Calcitonin-like receptor; DC: dendritic cells; 5-HT: 5-hydroxytryptamin; IENF: intraepidermal nerve fiber; IL-10: interleukin 10; LC: Langerhans cells; NEP: neutral endopeptidase; NF-kappaB: nuclear factor kappa B; NGF: Nerve growth factor; NK1: neurokinin 1; PAR-2: protease activated receptor-2; PGP 9.5: Protein gene product 9,5; PUVA: psoralen plus UVA; RAMP: Receptor activity modifying protein; SP: Substance P; TNF-alpha: Tumor necrosis factor alpha; TrkA: Tyrosin kinase A; UCA: Urocaic acid; UVA: Ultraviolet A; UVB: ultraviolet B, UVR: ultraviolet radiation; VR-1: vanilloid receptor 1;

Key Words: Photochemotherapy, Phototherapy, UV radiation, Sensory Nerve Fibers, CGRP, substance P, Nerve Growth Factor, Photoimmunology, Neurogenic Inflammation, Photoaging, Photocarcinogenesis, Review

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