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# Effect of Ultraviolet Light on the Release of Neuropeptides and Neuroendocrine Hormones in the Skin: Mediators of Photodermatitis and Cutaneous Inflammation

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**Ultraviolet (UV) irradiation of the skin causes both inflammation and alterations in the skin immune system. There is increasing experimental evidence that UV-induced skin inflammation is influenced by the sensory nervous system and the neuroendocrine system in the skin. The resulting complex network of cytokines, chemokines, neuropeptides, neuropeptide-degrading enzymes, neurohormones, and other inflammatory mediators mediate photodermatitis and cutaneous inflammation. Neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) are released from sensory nerves innervating the skin upon UV exposure. In addition, a variety of cells in the skin produce increased neuroendocrine hormones such as proopiomelanocortin (POMC) peptides and their receptors as well as neurotrophins after UV exposure. Neuropeptides and neurohormones are capable of directly or indirectly mediating**

**UV-induced cutaneous neurogenic inflammation by the induction of vasodilatation, plasma extravasation, and augmentation of UV-induced cytokine, chemokine, or cellular adhesion molecule expression required for activation and trafficking of inflammatory cells into the inflamed tissue. Neuropeptides and neurotrophins may also play a role in the repair of cutaneous UV injury. In addition to proinflammatory effects, UV-induced neuropeptides and neurohormones such as CGRP and  $\alpha$ -melanocyte-stimulating hormone may have immunosuppressive effects in the skin. This review will focus on the role that SP, CGRP, POMC peptides, and their receptors may play in modulating UV-induced inflammation in the skin. Key words: calcitonin gene-related peptide/proopiomelanocortin/skin immune system/substance P. *Journal of Investigative Dermatology Symposium Proceedings* 4:55-60, 1999**

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**E**xposure of the skin to UV irradiation causes erythema, edema, heat, and pain and profoundly influences the biologic functions of a variety of epidermal and dermal cells, including keratinocytes, melanocytes, Langerhans cells, mast cells, dermal fibroblasts, and endothelial cells. Biological, biochemical, and immunohistochemical studies reveal that these cells as well as skin-infiltrating inflammatory cells release pro-inflammatory and immunosuppressive cytokines, chemokines, growth factors, and neurohormones after UV irradiation, which creates a complex network of interacting inflammatory mediators. UV light has also been implicated in cutaneous carcinogenesis and in local as well as systemic immunosuppression, including impaired contact hypersensitivity (CHS), delayed-type hypersensitivity (DTH), and the induction of immunologic tolerance. These immunosuppressive responses have been attributed to cellular DNA damage, impaired

DNA repair, modulated intracellular signal transduction, impaired antigen-presenting function by Langerhans cells, dendritic cells (DC), or macrophages, or the induction of anti-inflammatory mediators such as the interleukin 1 receptor antagonist, IL-10, or  $\alpha$ -MSH (Kripke, 1990; Boonstra and Savelkoul, 1997; Garsen *et al*, 1997; Luger *et al*, 1997; Norris *et al*, 1997)

Afferent sensory nerves in the skin are another potential source of released inflammatory mediators after UV exposure. Unmyelinated C-fibers and myelinated A $\delta$ -fibers that are derived from dorsal root ganglions innervate the epidermis and the dermis and are capable of releasing a variety of neuropeptides upon noxious stimuli such as chemical, electrical, thermal, mechanical injury, and UV irradiation. Immunoreactivity for the tachykinins SP and neurokinin A (NKA), CGRP, vasoactive intestinal peptide, peptide histidine-isoleucinamide, neuropeptide Y, galanin, somatostatin, atrial natriuretic peptide and proopiomelanocortin (POMC) peptides such as  $\alpha$ - and  $\gamma$ -melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH),  $\beta$ -lipotropic hormone, or  $\beta$ -endorphin have been detected in human skin or skin cells (reviewed in Scholzen *et al*, 1998a; Luger *et al*, 1997).

Released neuropeptides in the skin not only function as neurotransmitters for pain and itch but also may act as mediators of immunity and inflammation. The inflammatory changes that are mediated by sensory nerves via the secretion of neuropeptides in a variety of tissues, including skin, are often referred to as neurogenic inflammation. Originally, the term neurogenic inflammation was used to describe a

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Abbreviations: ACTH, adrenocorticotropic hormone; CGRP, calcitonin gene-related peptide; MC-R, melanocortin receptor;  $\alpha$ -MSH,  $\alpha$ -melanocyte-stimulating hormone; NEP, neutral endopeptidase; NKA, neurokinin A; NK-R, neurokinin receptor; POMC, proopiomelanocortin; SP, substance P.

vascular response consisting of plasma extravasation and vasodilatation that occurred after electrical or chemical stimulation of sensory nerves. The tachykinins SP and NKA are primarily responsible for plasma extravasation, whereas CGRP and SP mediate vasodilatation (Delay-Goyet *et al*, 1992; Quartara and Maggi, 1998). According to the axon-reflex model of neurogenic inflammation, injury to tissues innervated by sensory nerves triggers an immediate signal to the dorsal root ganglion and the central nervous system (orthodromic response), which transmits the sensation of pain. A signal in the reverse direction (antidromic response) leads to the immediate release of neuropeptides in peripheral innervated tissues (Szolcsanyi, 1996). Receptors for neuropeptides released from these sensory nerves are found on a variety of nonimmune and immune cells. A broad range of target cell responses to SP, CGRP, and other neuropeptides have been described. The term neurogenic inflammation can be associated with diverse neuropeptide-induced activities such as mast cell degranulation, epithelial cell mediator secretion, and leukocyte activation, recruitment, vascular adhesion, and transmigration (Holzer, 1988; Ansel *et al*, 1996; Baluk, 1997; Scholzen *et al*, 1998a). The role of neuropeptides and neuroendocrine hormones in modulating the skin immune system following cutaneous UV irradiation will be the focus of this paper.

### NEUROPEPTIDES

**UV effects on the cutaneous sensory nervous system** Previous evidence for the participation of sensory nerves in UV-induced inflammation was derived from studies in rabbits demonstrating increased activity of nociceptive sensory nerves in the rabbit ear following UV irradiation that also increased the sensitivity of these nerves to other stimuli such as heat or bradykinin injection (Szolcsanyi, 1987). Electrophysiological and immunohistochemical studies have demonstrated that UV exposure of rat hindpaw skin resulted in spontaneous, long-lasting firing of sensory A- and C-fibers innervating the irradiated area and the development of prolonged behavioral hyperalgesia in response to thermal or mechanical stimuli (Thompson *et al*, 1994; Eschenfelder *et al*, 1995; Polgar *et al*, 1998). In addition, increased skin blood flow (erythema) was detected in the irradiated rat hindpaws and rat ears exposed to UV that was associated with a long-lasting increase in ear thickness (Eschenfelder *et al*, 1995). The observed UV-induced tissue reactions such as erythema and plasma extravasation were very similar to those demonstrated for antidromic nerve stimulation (Szolcsanyi, 1996). Among the neuropeptides released from sensory nerves in the skin, SP and CGRP appeared to be important mediators for UV-induced neuroinflammation of the skin. Immunohistochemical analysis of rat hindpaw skin after UV irradiation revealed a significant increase in SP and CGRP immunoreactivity and sensory nerve fibers 24 h post-irradiation (Eschenfelder *et al*, 1995).

The tachykinin SP belongs to a group of neuropeptides that includes SP, NKA, and neurokinin K, as well as the NKA-variants neuropeptide K and neuropeptide Y. In the skin, SP is released from sensory nerves that are in contact with microvascular endothelial cells, mast cells, hair follicles, and epidermal cells. The cellular effects of SP are mediated by the activation of a group of 7-transmembrane G-protein-coupled neurokinin receptors (NK-1R, NK-2R, and NK-3R). SP exhibits high-affinity binding for NK-1R, which is expressed on a variety of skin cells including keratinocytes, Langerhans cells, endothelial cells, and mast cells (Regoli *et al*, 1996; Scholzen *et al*, 1998a).

CGRP is a 37 amino acid peptide that is generated from the same gene locus as the calcium-regulating hormone calcitonin by tissue-specific, differential RNA splicing. CGRP is one of the most abundant neuropeptides in the skin and has been detected in C-fibers of sensory nerves associated with blood vessels as well as in free nerve endings in the skin contacting dermal mast cells, Merkel cells, melanocytes, keratinocytes, and Langerhans cells. CGRP activates two CGRP receptors subtypes (CGRP-1R and 2R), which also belong to the superfamily of G-protein coupled receptors and can be distinguished by their sensitivity to the peptide antagonist CGRP<sub>8-37</sub>. CGRP-1R was defined as being sensitive to this antagonist, whereas CGRP-2R was less sensitive (Emeson 1996; Hall and Brain, 1996; Scholzen *et al*, 1998a).

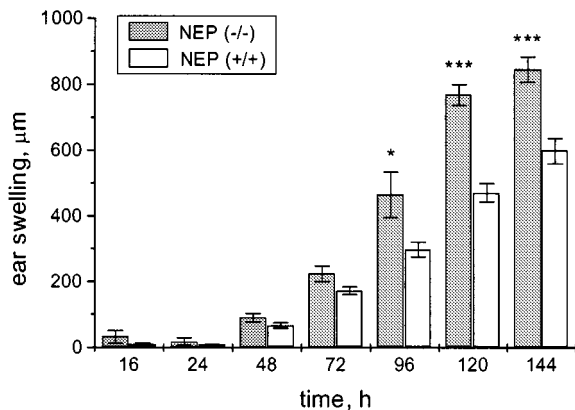
The release of SP and CGRP in the skin after UV irradiation is of particular interest because SP and CGRP alter a number of biologic functions of skin cells during cutaneous neuroinflammation, including cytokine and chemokine production, cell proliferation, cellular adhesion molecule expression, and immunocompetent and antigen-presenting cell (APC) functions (Ansel *et al*, 1996; Lambert and Granstein, 1998; Scholzen *et al*, 1998a). For example, SP stimulates the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in the skin and both SP and CGRP enhance the functional adhesion of particular leukocytic cell lines to human dermal microvascular endothelial cells (HDMEC) *in vitro* (Quinlan *et al*, 1998, 1999).<sup>1</sup> Thus, because they are coreleased from sensory nerves in the skin, SP and CGRP may act synergistically in modulating cutaneous inflammatory responses in epidermal and dermal cells after UV exposure.

### Neuropeptide participation in UV-induced cutaneous edema and erythema

There is considerable experimental data to suggest that neuropeptides may play an important role in the edema and erythema that develop following UV irradiation of the skin by their direct ability to influence vasodilation and microvascular permeability of blood vessels in the skin and by their ability to influence mast cell function. One of the most prominent effects of CGRP *in vivo* appears to be its vasodilatory action and its capability to potentiate microvascular permeability and edema formation caused by other neuropeptides. Intradermal injection of CGRP caused long-lasting erythema even in femtomolar to picomolar doses (Brain, 1996). SP is well known to provoke erythema and edema via a mast cell-dependent and a mast cell-independent pathway. Interestingly, *in vitro* studies using rat peritoneal mast cells demonstrated that UV does not have a direct impact on histamine release from these cells. Moreover, these studies indicate that SP-induced release of histamine, which is known to cause vasodilatation via activation of H1 receptors on vascular smooth muscle cells, could be inhibited in a dose-dependent manner by pretreatment of mast cells with UV (Amano *et al*, 1997). These data, however, are not necessarily in conflict with the observation that UV exposure results in vasodilatation and plasma extravasation. Because elevated histamine levels were detected up to 8 h after UV (Gilchrest *et al*, 1981), the mast cell-dependent vasodilatation and plasma extravasation involving SP-induced mast cell histamine release may only be of importance for an immediate increase in microcirculation and plasma extravasation after UV (Columbo *et al*, 1996). In another study, the presence of nerves with histamine immunoreactivity has been demonstrated in rat skin, suggesting the existence of a mast cell-independent mechanism for vasodilatation via nerve-derived histamine (Johansson *et al*, 1995). Recently, it has also been demonstrated that intradermal injection of the SP antagonist spantide as well as the epicutaneous application of the NK-1R antagonist CP-96 345 significantly reduced the UV-induced ear swelling response as well as the skin blood flow in rat (Benrath *et al*, 1995a; Benrath *et al*, 1995b). Injection of the CGRP antagonist CGRP<sub>(8-37)</sub> attenuated skin blood flow, but did not prevent the development of edema after UV. Because increased nitric oxide (NO) synthase activity in nerve fibers in the UV-exposed area of rat skin has been detected (Benrath *et al*, 1995a), these and other studies (Goldsmith *et al*, 1996; Kakuyama *et al*, 1998) also suggest that UV-induced NO release from sensory nerves may participate in the vascular component of UV-induced neuroinflammation. In addition to its direct vasodilatory action it has been proposed that NO may be necessary for either the release of CGRP from sensory nerves or its subsequent activity (Holzer *et al*, 1995). Thus, UV-induced CGRP, SP, and NO may contribute to the prolonged edema and erythema that develop after UV irradiation (Bowden *et al*, 1996).

The role of cutaneous neuropeptides in UV-induced edema is also supported by recent studies in our laboratory using genetically engineered mice deficient for neutral endopeptidase (NEP), the

<sup>1</sup>Scholzen TE, Burbach G, Song IS, *et al*: CGRP induction of human dermal microvascular endothelial cell (HDMEC) chemokine expression and functional adhesion of leukocytes to HDMEC *in vitro*. *Arch Dermatol Res* 291:116, 1999 (abstr.)



**Figure 1. Photodermatitis in NEP(-/-) and NEP(+/+) mice.** NEP(-/-) or NEP(+/+) mice were exposed to a single whole body dose of 1.2 J UVB light (Westinghouse FS/20 bulbs) per m<sup>2</sup>. The ear swelling response was determined over time from 16 to 144 h post-irradiation. All values are given in µm as mean ± SEM, n = 5. \*p < 0.05, \*\*\*p < 0.001 for NEP(-/-) mice versus NEP(+/+) mice.

principal SP-degrading peptidase. NEP(-/-) mice, in contrast to wild-type NEP(+/+) animals, demonstrated a significantly increased ear swelling after UVB irradiation (Fig 1) that was histologically accompanied by an increased cutaneous inflammatory infiltrate. These studies support the concept that the final biologic response of a given neuropeptide requires not only the presence of the neuropeptide and its corresponding receptor on the target cells in the skin, but also the presence of neuropeptide-degrading enzymes such as NEP.

**Neuropeptide modulation of pain sensation after UV exposure** There is evidence that UV irradiation of the skin may also lead to alterations in neuropeptide levels in the peripheral nervous system that contribute to altered pain sensation. A- and C-fibers prepared from rat spinal cords after induction of peripheral injury by UV irradiation demonstrated increased evoked responses that coincided with hyperalgesia. The increased excitability of nerve fibers could be blocked by NK-1R and NK-2R antagonists (Thompson *et al*, 1994; Eschenfelder *et al*, 1995). In addition, repeated exposure of rat hindpaw to UV induced a complex pattern of changes in the spinal SP immunoreactivity, suggesting that an increased SP production in DRG neurons was not restricted to the segments that innervate the inflamed area (Polgar *et al*, 1998). Analysis of neural CGRP expression paralleled the SP findings by also demonstrating a long-term increase of CGRP levels in the rat spinal horn following UV exposure (Gillardon *et al*, 1992). These studies imply that noxious noninvasive stimuli such as UV are capable of altering the synaptic transmission and central pain sensation by modulating the neuropeptide content of sensory nerves. The latter may be responsible for the development of inflammatory tissue hyperalgesia during UV-induced inflammation.

**The effect of neuropeptides and neurotrophins on repair of cutaneous UV injury** An increasing number of studies have shown that sensory innervation affects tissue repair and wound healing (Ansel *et al*, 1996). For example, the surgical resection of cutaneous nerves as well as certain sensory defects leads to impaired wound healing or the development of nonhealing ulcers (Ansel *et al*, 1996). On a cellular level, SP, CGRP, and NKA have been reported to enhance the proliferation of keratinocytes, melanocytes, fibroblasts, and endothelial cells *in vitro*, to induce neovascularization *in vivo*, and to promote the release of growth factors (Ansel *et al*, 1996). In addition, topical application of the NK-1R antagonist CP-96 345 significantly delayed wound healing in UV-injured rat skin (Benrath *et al*, 1995b). It has also been reported that UV irradiation can induce epidermal neurotrophins such as nerve growth factor (NGF) (Gillardon *et al*, 1995; Gilchrist *et al*, 1996; Bayerl *et al*, 1997) that are known to promote nerve regeneration and reinnervation of the skin, and to protect epidermal cells from UV-induced apoptotic cell death (Ansel *et al*, 1996; Tron *et al*, 1990; Zhai *et al*, 1996). The release of NGF

after UV may be secondary to UV-induced neuropeptides because both NKA and SP are capable of inducing NGF expression in keratinocytes.<sup>2</sup> Thus, these findings indicate that endogenous neuropeptides may have a trophic function in tissue damage after UV exposure.

**Neuropeptide participation in UV-induced immunosuppression** In addition to proinflammatory effects, UV exposure of the skin results in a variety of immunosuppressive effects such as impaired CHS or DTH reactions and the induction of tolerance. These effects have been linked to alterations in epidermal and dermal APC including Langerhans cells, dermal DC, and macrophages that may be mediated directly or indirectly by UV-released soluble factors like IL-10, TNFα, or urocanic acid (Kondo *et al*, 1994; Kurimoto and Streilein, 1992; Beissert *et al*, 1996). The role of neuropeptides in UV-induced immunosuppression is supported by a number of recent investigations. Several studies have linked the UV-induced suppression of DTH and CHS reactions to released CGRP and the neuroendocrine hormone α-MSH. CGRP is released from peripheral sensory nerves after UV exposure from neurons that are in intimate contact with epidermal Langerhans cells and mast cells. CGRP has been found to reduce Langerhans cells density and locally impair Langerhans cell and dermal DC functions (Yoshikawa and Streilein, 1990; Niizeki *et al*, 1997). Additional evidence for the role of CGRP in mediating UV-induced CHS and DTH suppression is derived from studies using cultured Langerhans cell and Langerhans cell lines. It was found that CGRP inhibited both proliferation and antigen presentation by peripheral blood mononuclear cells and Langerhans cells (Fox *et al*, 1997). This may be due in part to upregulation of anti-inflammatory cytokines such as IL-10 that are capable of suppressing T cell functions. Additionally, downregulation of pro-inflammatory cytokines (IL-1 and IL-12) by CGRP as well as suppression of the costimulatory molecule CD86, but not CD80, on Langerhans cells or macrophages may inhibit T cell activation (Torii *et al*, 1997; Lambert *et al*, 1998).

In summary, these *in vitro* and *in vivo* observations support the possibility that SP and CGRP can directly or indirectly modulate UV-induced cutaneous inflammation by the (i) induction of vasodilatation and plasma extravasation; (ii) modulation of UV-induced cytokine and chemokine release; (iii) regulation of microvascular endothelial cellular adhesion molecule expression; and (iv) mediation of pain sensation following UV irradiation. CGRP also appears to have immunosuppressive properties primarily by impairing antigen-processing and presentation.

## NEUROENDOCRINE HORMONES

**The effect of UV irradiation on proopiomelanocortin peptides and melanocortin receptors in the skin** It has been established that the skin is a source and target of neuroendocrine hormones of the proopiomelanocortin (POMC) family, including α-, β-, γ-MSH, ACTH, β-LPH, or β-END. Expression and release of these peptides has been detected in normal murine or human keratinocytes, melanocytes, Langerhans cells, and fibroblasts as well as by transformed keratinocyte and melanocyte cell lines *in vitro*. Most of these peptides have also been identified by immunohistochemical staining in both murine and human skin *in vivo*.

POMC peptides exert their effects by activating specific melanocortin receptors (MC-1R-5R) that belong to the G-protein-coupled receptor superfamily. The most abundant MC-R in the skin is MC-1R, which exhibits high affinity for α-MSH and ACTH (Table I). Recent studies with both keratinocytes and dermal microvascular endothelial cells indicate that prominent regulators of MC-1R expression in the skin are IL-1β and α-MSH (Cone *et al*, 1996; Luger *et al*, 1997). There is increasing evidence that UV irradiation may play an important role in regulating the production and the post-translational processing of POMC as well as MC-1R expression. POMC mRNA and peptides including α-MSH, ACTH, β-LPH, and β-END can be upregulated by UV or IL-1 in human melanocytes, melanoma cells, keratinocytes,

<sup>2</sup>Burbach GJ, Kim KH, Song IS, *et al*: Cutaneous neuropeptide induction of keratinocyte nerve growth factor. *J Invest Dermatol* 112:533, 112, 1999 (abstr.)

**Table I. Expression of MC-R and their specific ligands**

Receptor	Tissue/cellular source	Specific ligand
MC-1R	melanocytes monocytes macrophages mast cells keratinocytes fibroblasts	$\alpha$ -MSH, ACTH
MC-2R	adrenal tissues, brain adipocytes	ACTH, $\alpha$ -, $\beta$ -, $\gamma$ -MSH
MC-3R	brain, placenta, gut	heptapeptide core of ACTH, $\alpha$ -, $\beta$ -, $\gamma$ -MSH
MC-4R	brain	ACTH, $\alpha$ -, $\beta$ -, $\gamma$ -MSH, $\beta$ -LPH
MC-5R	skeletal muscle, brain, spleen, thymus, adipocytes	ACTH, $\alpha$ -, $\beta$ -, $\gamma$ -MSH

HDMEC, and some epidermoid carcinoma cell lines (Schauer *et al*, 1994; Chakraborty *et al*, 1995, 1996; Wintzen and Gilchrist, 1996).

Numerous studies indicate that in the pituitary POMC expression and post-translational POMC prohormone processing occurs in a cell- and tissue-specific manner involving prohormone convertases (PC-) 1 and 2. The expression of these PC seemed to be restricted to cells of endocrine and neuroendocrine origin (Castro and Morrison, 1997) and relatively little is known about the post-translational processing of the inactive POMC prohormone in nonpituitary tissues, including skin. Reverse transcriptase-polymerase chain reaction studies indicate that keratinocytes, certain epidermoid cell lines, and HDMEC express PC-1 mRNA (Brzoska *et al*, 1997). UV light, IL-1, and  $\alpha$ -MSH itself are capable of regulating the mRNA expression of PC. Although  $\beta$ -endorphin and  $\alpha$ -MSH can be detected in keratinocytes and  $\alpha$ -MSH can be detected in HDMEC, only the mRNA for the PC-2-activating protein 7B2 could be detected in these cells (Scholzen *et al*, 1999). Whereas PC-2 expression is required for processing POMC in pituitary cells, an alternative proteolytic pathway for POMC processing in skin cells may exist that could involve neutral endopeptidase (NEP) or a peptidase that has not yet been identified (Castro *et al*, 1989; Smith *et al*, 1992).

UV light can also induce the production of cytokines such as IL-1 and IL-6 in skin cells (Luger and Schwarz, 1995; as well as simultaneously upregulating the expression of both POMC and PC-1 in these skin cells. Because MC-1R expression is upregulated by IL-1 and/or UV-light in melanocytes, keratinocytes, and HDMEC (Brzoska *et al*, 1997; Hartmeyer *et al*, 1997), these same mediators may increase the sensitivity of certain cutaneous or noncutaneous target cells for POMC peptides by upregulating MC-1R expression (Brzoska *et al*, 1997). Another potential mechanism for cutaneous POMC induction is derived from studies demonstrating that murine and human skin express mRNA for corticotrophin releasing hormone (CRH) and CRH receptors. CRH receptors are upregulated in human keratinocytes and melanocytes following UVB irradiation (Slominski *et al*, 1995, 1996). Hypothalamus-derived CRH, like IL-1 or IL-6, is an important stimulus for POMC expression in the pituitary or in pituitary cells *in vitro*. Consequently, it has been proposed that an equivalent of the hypothalamic-pituitary-adrenal (HPA) axis exists in the skin. The conservation of this important link between the HPA axis as central regulatory unit for a coordinated response to exogenous stress and the immune system may be of importance for the cutaneous response to injury after exposure to external agents such as UV irradiation. These findings have a number of implications regarding potential mechanisms that could be involved in protection of the skin from UV, the repair of photodamaged skin, alterations of biologic functions of epidermal and dermal cells, and local or systemic immunomodulation via POMC peptides, in particular by  $\alpha$ -MSH.

#### $\alpha$ -MSH protection in response to cutaneous UV exposure

Various *in vivo* and *in vitro* studies demonstrate the participation of  $\alpha$ -MSH and MC-R in UV-induced melanogenesis. Melanogenesis represents one of the most important protection mechanisms against

harmful effects of UV and includes the increase in melanocyte density, melanin biosynthesis, and transfer of pigment granules to surrounding keratinocytes. These studies demonstrated that melanocytes can specifically respond to ACTH and  $\alpha$ - and  $\beta$ -MSH. UV-induced POMC peptides could either activate melanocyte melanogenesis via MC-R activation or "prime" these cells for UV-induced melanogenesis. MSH-induced cAMP formation in melanocytes appears to be an obligatory step for melanogenic responses to UVB (Pawelek *et al*, 1992; Suzuki *et al*, 1996; Im *et al*, 1998).

**Potential immunomodulatory effects of POMC peptides in photodermatitis** Among POMC-peptides,  $\alpha$ -MSH is regarded as the neurohormone with a broad range of immunomodulatory capacities.  $\alpha$ -MSH can act centrally within the brain to inhibit local inflammation and peripheral inflammation. This neurohormone can also act locally in the skin by inhibiting the production and function of certain pro-inflammatory cytokines, upregulating anti-inflammatory mediators, and inhibiting inflammatory actions of cutaneous immunocompetent cells (Luger *et al*, 1998; Lipton and Catania, 1998). In the skin, POMC peptides are capable of modulating cytokine, chemokine, and adhesion molecule expression in keratinocytes, melanocytes, fibroblasts,<sup>3</sup> and HDMEC<sup>4</sup> (Hartmeyer *et al*, 1997; Luger *et al*, 1998; Morandini *et al*, 1998). Recent studies also revealed that  $\alpha$ -MSH can downregulate the LPS or TNF $\alpha$ -induced expression of E-selectin and VCAM-1 as well as the functional adhesion of T- or B-lymphoblastoid cell lines to HDMEC *in vitro*. Interestingly,  $\alpha$ -MSH alone had a dose-dependent stimulatory effect on the lymphocyte-endothelial cell interaction (Scholzen *et al*, unpublished observations). Thus, it can be speculated that the stimulatory effect of  $\alpha$ -MSH on leukocyte recruitment may assist in the initiation of inflammatory responses to UV. In contrast,  $\alpha$ -MSH could also inhibit the recruitment of inflammatory cells by activated endothelium during the late phase of photodermatitis and thus suppress cutaneous inflammation. Recent studies also indicated that some of these  $\alpha$ -MSH anti-inflammatory properties may be mediated via downregulation of cellular NF- $\kappa$ B activity<sup>5,6</sup> (Manna and Aggarwal, 1998).

**POMC peptides and UV-induced immunosuppression** *In vivo*  $\alpha$ -MSH can impair CHS and DTH reactions by inhibiting both the sensitization and the elicitation phases of these responses and by inducing hapten-specific tolerance in mice (Grabbe *et al*, 1996). UV-induced IL-10 can have similar immunosuppressive effects as  $\alpha$ -MSH (Enk *et al*, 1995). Because  $\alpha$ -MSH stimulation can increase the *in vitro* IL-10 production in human monocytes (Bhardwaj *et al*, 1996, 1997), it may be that IL-10 induction by  $\alpha$ -MSH mediates some of the immunosuppressive effects of UV. In addition,  $\alpha$ -MSH can inhibit IFN $\gamma$  production in T lymphocytes and downregulate the costimulatory molecule CD86, but not CD80, on monocytes and peripheral blood-derived DC (Bhardwaj *et al*, 1997).<sup>7</sup> In this respect, the activity of  $\alpha$ -MSH strongly resembles that of CGRP and thus may contribute to the UV-mediated downregulation of pro-inflammatory molecules, induction of immunosuppressive cytokines, and inhibition of APC activation.

#### CONCLUSION

UV irradiation can modulate the production of cutaneous cytokines, chemokines, neuropeptides, neuropeptide-degrading enzymes, neuro-

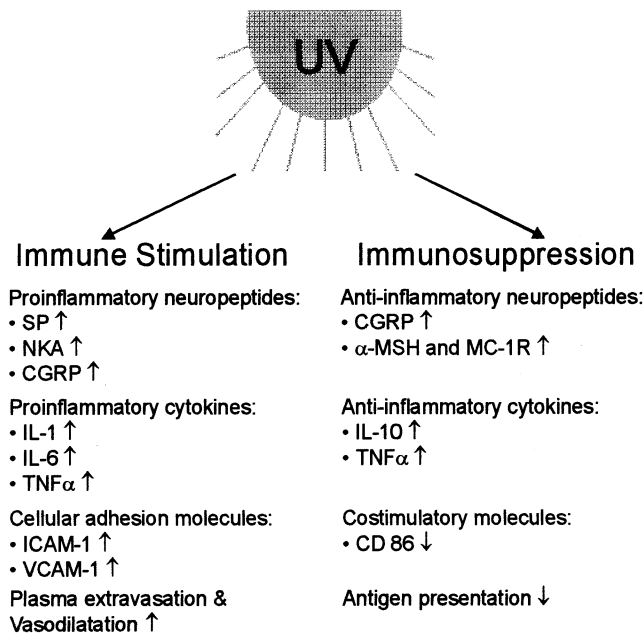
<sup>3</sup>Schulte U, Becher E, Kalden D-H, *et al*: Evidence for a functional melanocortin receptor on human fibroblasts. *J Invest Dermatol* 110:479, 1998 (abstr.)

<sup>4</sup>Scholzen T, Kalden D-H, Luger T A, Armstrong C A, Ansel JC:  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH) modulates TNF $\alpha$  or IL-1 $\beta$ -induced production of interleukin-8 and GRO $\alpha$  by human dermal microvascular endothelial cells. *Arch Dermatol Res* 290:104, 1998 (abstr.)

<sup>5</sup>Brzoska T, Kalden D-H, Scholzen T, *et al*:  $\alpha$ -melanocyte stimulating hormone downregulates IL-1 mediated target gene expression by attenuation of NF- $\kappa$ B activation. *J Invest Dermatol* 110:495, 1998 (abstr.)

<sup>6</sup>Kalden D-H, Fastrich M, Brzoska T, *et al*: Alpha-melanocyte-stimulating hormone reduces endotoxin-induced activation of nuclear factor- $\kappa$ B in endothelial cells. *J Invest Dermatol* 110:495, 1998 (abstr.)

<sup>7</sup>Becher E, Mahnke K, Brzoska T, Schwarz T, Luger TA: Human monocyte-derived dendritic cells express a functional  $\alpha$ -MSH receptor - downregulation of accessory molecule expression by  $\alpha$ -MSH. *Arch Dermatol Res* 290:88, 1998 (abstr.)



**Figure 2.** Immunostimulatory and immunosuppressive effects in the skin mediated by UV light.

trophins, and other inflammatory mediators that link the cutaneous immune, the sensory nervous, and the neuroendocrine system. By inducing cytokines, cutaneous neuropeptides, and neuroendocrine hormones such as SP, CGRP, and  $\alpha$ -MSH, UV irradiation can initiate or amplify the inflammatory response in acute photodermatitis. Some of these mediators also suppress the cutaneous inflammatory response to UV irradiation (Fig 2). To date it is not clear how and where pro- and anti-inflammatory signals derived from sensory neurons and skin cells after UV exposure are integrated to result in a final biologic response.

Thus, on the one hand UV exposure leads to the release of pro-inflammatory factors and on the other hand UV also induces the production of mediators such as  $\alpha$ -MSH and CGRP, which have immunosuppressive effects. As in all inflammatory responses there is a complex interaction and interdependent biologic response to UV with both proinflammatory and anti-inflammatory agents coreleased in the affected tissue. The relative balance and activities of these factors will determine the clinical outcome of the host response. Inflammation serves as a critical early, rapid innate host immune response to a variety of microbial and nonmicrobial agents. In highly evolved hosts such as man, the inflammatory response seeks to neutralize and isolate these foreign agents, while the cognate immune system is activated and mobilized. All goes well with this scenario unless the offending agents cannot be eliminated and/or if the inflammatory process continues unabated. To prevent the latter, a variety of mechanisms have evolved that check the persistent inflammatory process. These include the rapid desensitization of target cells responding to the inflammatory mediators, the presence of numerous proteolytic enzymes to degrade peptide mediators, and the release of anti-inflammatory factors such as IL-10, TGF- $\beta$ ,  $\alpha$ -MSH, and in some cases CGRP. These anti-inflammatory agents are often released in response to specific inflammatory molecules. Therefore, they do not prevent the initial important host inflammatory response, but rather they serve to dampen this response and prevent it from continuing for a prolonged period of time, which would have detrimental consequences for the host. Thus, it appears that UV neuroinflammation follows the same general paradigm as other types of inflammation. Progress in understanding how neuropeptides and neuroendocrine hormones participate and interact on a molecular and cellular basis in the UV modulation of the skin immune system is essential to improved understanding of both the beneficial effects of

UV in clinical treatment of certain skin diseases such as psoriasis, and the mechanisms of skin carcinogenesis after UV exposure.

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