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Neuronal Control of Skin Function: The Skin as a Neuroimmunoendocrine Organ

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Roosterman, Dirk, Tobias Goerge, Stefan W. Schneider, Nigel W. Bunnett, and Martin Steinhoff. Neuronal Control of Skin Function: The Skin as a Neuroimmunoendocrine Organ. *Physiol Rev* 86: 1309–1379, 2006; doi:10.1152/physrev.00026.2005.—This review focuses on the role of the peripheral nervous system in cutaneous biology and disease. During the last few years, a modern concept of an interactive network between cutaneous

nerves, the neuroendocrine axis, and the immune system has been established. We learned that neurocutaneous interactions influence a variety of physiological and pathophysiological functions, including cell growth, immunity, inflammation, pruritus, and wound healing. This interaction is mediated by primary afferent as well as autonomic nerves, which release neuromediators and activate specific receptors on many target cells in the skin. A dense network of sensory nerves releases neuropeptides, thereby modulating inflammation, cell growth, and the immune responses in the skin. Neurotrophic factors, in addition to regulating nerve growth, participate in many properties of skin function. The skin expresses a variety of neurohormone receptors coupled to heterotrimeric G proteins that are tightly involved in skin homeostasis and inflammation. This neurohormone-receptor interaction is modulated by endopeptidases, which are able to terminate neuropeptide-induced inflammatory or immune responses. Neuronal proteinase-activated receptors or transient receptor potential ion channels are recently described receptors that may have been important in regulating neurogenic inflammation, pain, and pruritus. Together, a close multidirectional interaction between neuromediators, high-affinity receptors, and regulatory proteases is critically involved to maintain tissue integrity and regulate inflammatory responses in the skin. A deeper understanding of cutaneous neuroimmunoendocrinology may help to develop new strategies for the treatment of several skin diseases.

I. INTRODUCTION

Substantial evidence has accumulated that the cutaneous peripheral nervous system (PNS) plays a pivotal role in skin homeostasis and disease. First, the innervated skin is a crucial barrier protecting the body from danger from the "external environment." Cutaneous nerves also respond to stimuli from the circulation and to emotions ("internal trigger factors"). Moreover, the central nervous system (CNS) is directly (via efferent nerves or CNS-derived mediators) or indirectly (via the adrenal glands or immune cells) connected to skin function (Fig. 1).

Sensory as well as autonomic (sympathetic) nerves influence a variety of physiological (embryogenesis, vasocontraction, vasodilatation, body temperature, barrier function, secretion, growth, differentiation, cell nutrition, nerve growth) and pathophysiological (inflammation, immune defense, apoptosis, proliferation, wound healing) functions within the skin. In unstimulated nerves, neuromediators are barely detectable within the skin tissues. Upon direct stimulation by physical stimuli (thermal, ultraviolet light, mechanical, electrical), chemical, or indirect stimuli such as allergens, haptens, microbiological agents, trauma, or inflammation, a significant increase of regulatory neuropeptides, neurotrophins, neurotransmitters, or oxygen products (e.g., nitric oxide) can be detected in vitro and in vivo. Thus mediators derived from sensory or

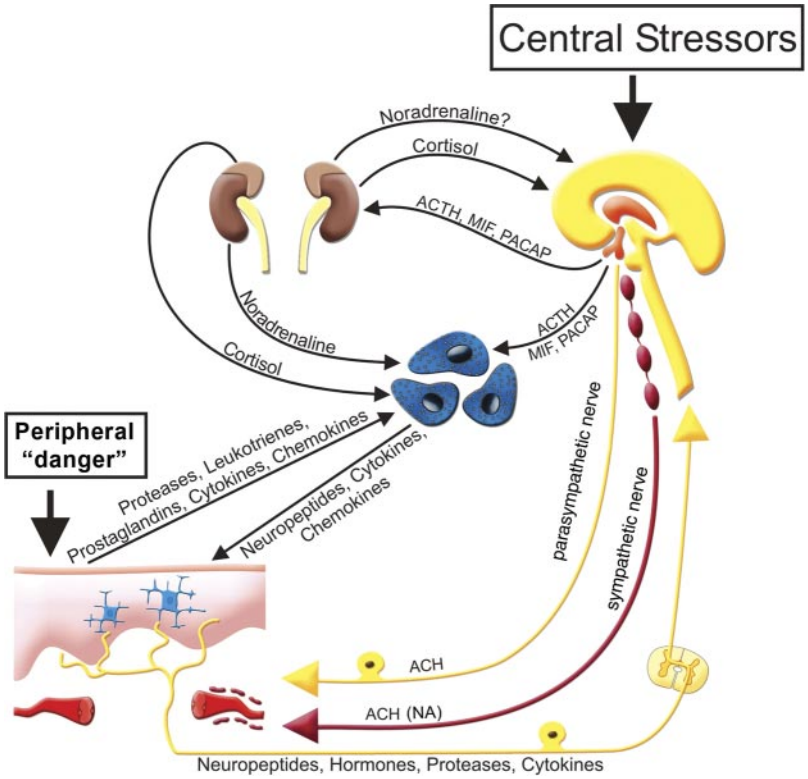

FIG. 1. The skin as a neuroimmunoendocrine organ. The skin is associated with the peripheral sensory nervous system (PNS), the autonomous nervous system (ANS), and the central nervous system (CNS). *1*) Various stressors activate the hypothalamus/hypophysisis within the CNS which results in the *2*) release of neuromediators such as corticotropin-releasing hormone (CRH), melanocyte stimulating hormone (MSH), pituitary adenylate cyclase activating polypeptide (PACAP), or MIF, for example. They may stimulate either the release of *3*) norepinephrine and cortisol from the adrenal glands or *4*) directly stimulate leukocytes in the blood system via CRH, MC, or PAC receptors, thereby modulating immune responses during inflammation and immunity. Norepinephrine and cortisol effect several immune cells including lymphocytes, granulocytes, and macrophages. *5*) Immune cells release cytokines, chemokines, and neuropeptides that modulate inflammatory responses in the skin. *6*) Upon stimulation, sensory nerves release neuromediators (Fig. 2, Table 2) that modulate cutaneous inflammation, pain, and pruritus. Skin inflammation affects activation of immune cells via cytokines, chemokines, prostaglandins, leukotrienes, nitric oxide, and MSH (see Table 2 for details), which may have a proinflammatory [e.g., substance P (SP)] or anti-inflammtory effect [e.g., calcitonin gene-related peptide (CGRP), PACAP] by upregulating or downregulating inflammatory mediators such as cytokines or tumor necrosis factor (TNF)-α, for example. *7*) Autonomous nerves, in the skin mainly sympathetic cholinergic and rarely parasympathetic cholinergic nerves innervate several cells in the skin, thereby maintaining skin homeostasis and regulating inflammation as well as host defense (see Fig. 4 for details).

autonomic nerves may play an important regulatory role in the skin under many physiological and pathophysiological conditions. Beside the periphery, however, a subtle complex communication network exists between the spinal cord, the CNS, and the immunoendocrine system. Figure 1 summarizes the mediators involved in regulating the neuroimmunoendocrine network.

II. ANATOMY AND PHYSIOLOGY OF THE CUTANEOUS NERVOUS SYSTEM

A. Neuroanatomy and Neurophysiology of Cutaneous Nerves

The anatomy and classification of cutaneous sensory nerves has been extensively reviewed by Winkelmann (940). According to the classification of Halata, sensory nerves are based on two groups: the epidermal and the dermal skin-nerve organs. Both can be subdivided: the epidermal skin-nerve organs consist of "free" nerve endings or hederiform nerve organs (e.g., Merkel cells). The term *free* terminal nerve ending refers to a slight axon expansion that still contains perineural cells including cytoplasm of Schwann cells and multiple cell organelles (459, 881). In the dermal part, free sensory nerve endings, the hair nervous network (Pinkus discs), and the encapsulated endings [Ruffini, Meissner, Krause, Vater-Pacini (vibration), mucocutaneous end organ] have to be differentiated (Table 1). Neurophysiological studies have led to a more advanced functional classification of sensory nerves based on the type of cutaneous mechanoreceptor responses (Table 1).

Sensory nerves can be subdivided into four groups: Aα fibers (12–22 mm) are highly myelinated, show a fast conduction velocity (70–120 m/s), and are associated with muscular spindles and tendon organs. Aβ fibers are moderately myelinated (6–12 μm) and capture touch receptors. Aδ fibers constitute a thin myelin sheath (1–5 μm), an intermediate conduction velocity (4–30 m/s), and are generally polymodal. The slow-conducting C fibers (0.5–2 m/s) are unmyelinated and small (0.2–1.5 μm). Aδ fibers constitute ~80% of primary sensory nerves sprouting from dorsal root ganglia, whereas C fibers make up ~20% of the primary afferents (14, 470). Moreover, the activation threshold of Aδ fibers is higher than that of C fibers.

In human peripheral nerves, 45% of the cutaneous afferent nerves belong to a subtype of sensory nerves that are mechano-heat responsive C fibers (C-m^+h^+) (729). However, only 13% of these nerves were found to be only mechanosensitive (C-m^+), 6% were heat sensitive (C-h^+), 24% were neither heat nor mechanoresponsive (C-m^-h^-), and ~12% were of sympathetic origin; 58% of C-m^+h^+ responded to mustard oil, and 30% of C-m^+ or C-m^-h^- did so (729).

Both C and Aδ fibers respond to a variable range of stimuli such as physical (trauma, heat, cold, osmotic changes, distension or mechanical stimulation, ultraviolet light) as well as chemical (toxic agents, allergens, proteases, microbes) agents (reviewed in Ref. 811). However, although Aδ fibers can also respond to chemical stimuli, their role in neurogenic inflammation and pruritus is still poorly understood.

On the molecular level, specific receptor distribution seems to be important for the various functions of sensory nerve subtypes. For example, mechanoreceptors exclusively express the T-type calcium channel Ca(v)3.2 in the dorsal root ganglion (DRG) of D-hair receptors. Pharmacological blockade indicates that this receptor is important for normal D-hair receptor excitability including mechanosensitivity (758). However, different mechanisms seem to underlie mechanosensory function in various tissues. In the gut and skin, for example, the de-

TABLE 1. *The neurophysiological characteristics of sensory nerves in the skin*

Category	Stimulus	Physiological Type	Anatomy Type	Nerve Type	Sensation
Low-threshold mechanoreceptors	Displacement	Type I	Hair disc	A	?
		SA I	Merkel cell complex	A	Pressure
		Type II	? Ruffini ending	A	?
		SA II		A	?
	Displacement velocity	GI hair	Hair palisade	A	Hair movement
		RA field receptor	Meissner corpuscle	A	Tapping
		D hair	Hair follicle	A	?
		C mechanoreceptor	Nerve network?	C	?
	Vibrations	Pacinian corpuscle	Pacinian corpuscle Nerve network	A	Buzzing
Thermoreceptors	Cooling	Cold receptor	Nerve network	C, A	Cold
	Warming	Warm receptor	Nerve network	C	Warm
Nocireceptors	Noxious deformation	Myelinated		A	Sharp pain
	Noxious heat, chemicals	Unmyelinated		C	Dull pain, sharp pain, burning pruritus

generin/epithelial Na^+ channel (DEG/ENaC) ion channel ASIC1 influences visceral but not skin mechanosensation (612).

Inflammation and trauma induce the activation and/or sensitization of nociceptors (769, 770). During chronic inflammation, pain, or pruritus, prolonged nociceptor activation may occur, thereby increasing the sensitivity of nociceptors which may lead to the perpetuation of neuronal stimulation and thus progression.

In the skin, cutaneous nerve fibers are principally sensory, with an additional complement of autonomic nerve fibers (114, 563). In contrast to sensory nerves, autonomic nerves never innervate the epidermis in mammals. Sensory nerves innervate the epidermis and dermis as well as the subcutaneous fatty tissue as a three-dimensional network (425, 881, 951). Most of the nerve fibers are found in the mid-dermis and the papillary dermis. The epidermis, blood vessels, and skin appendages such as hair follicles, sebaceous glands, sweat glands, and apocrine glands are innervated by several subtypes of sensory nerves (622, 811).

Regional-specific differences can be observed with respect to the mucocutaneous border, the glabrous skin, and hairy skin (940). With the use of electron microscopy (336), confocal laser scan microscopy (671), and immunohistochemistry (809), it is possible to demonstrate that the epidermis is also innervated by a three-dimensional network of unmyelinated C fibers with free-branching endings that arise in the dermis and their basement membrane apposed to epidermal cells such as keratinocytes, melanocytes, Langerhans cells, and Merkel cells, respectively. Increased epidermal innervation has been described in skin lesions of various inflammatory skin diseases (379, 383, 633, 640, 761, 809), wound repair (234), skin cancer (232, 447, 552, 567, 765), epithelial hyperplasia (702), after exposure to ultraviolet (UV) light, or during psoralen UVA therapy (525, 785).

B. The "Skin-Sensory PNS-CNS Connection" Exemplified by Itching

The skin is innervated by afferent somatic nerves with fine unmyelinated (C) or myelinated (Aδ) primary afferent nerve fibers transmitting sensory stimuli (temperature changes, chemicals, inflammatory mediators, pH changes) via dorsal root ganglia and the spinal cord to specific areas of the CNS, resulting in the perception of pain, burning, burning pain, or itching (Table 1, Fig. 2) (see sect. II*B* for details). Thus the skin "talks" to the brain via primary afferents thereby revealing information about the status of peripherally derived pain, pruritus, and local inflammation.

Recent studies on the pathophysiology of pruritus reveal the complexity of the bidirectional network be-

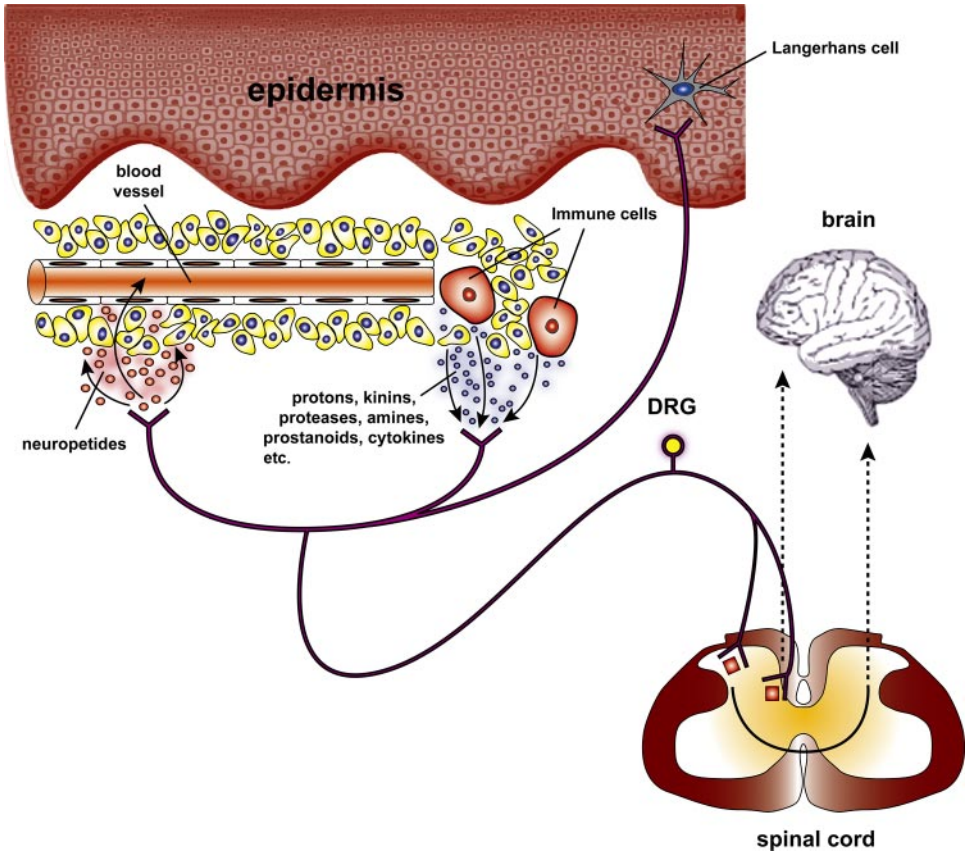

FIG. 2. Mediators and sensitization pattern of nociceptive and pruriceptive neurons in the skin. Sensitizing and activating mediators in the skin target receptors on primary afferent nerve fibers involved in itch and pain processing. During inflammation, mechanoinsensitive "sleeping" nociceptors and itch histamine-sensitive mechanoinsensitive puriceptors and probably mechanosensitive puriceptors transmit the response to the spinal cord. In the spinal cord noxious input can induce central sensitization for pain, and puriceptive input can provoke central sensitization for itch. Via the contralateral tractus spinothalamicus, the stimuli from primary afferent sensory nerves will be transmitted to specific areas in the CNS (see sect. II for details).

tween the PNS and CNS. In pruritus, skin-derived itch-selective primary afferent fibers are connected with specific units within the lamina I of the spinal cord (Fig. 2). Here, they form a distinct pathway projecting to the posterior part of the ventromedial thalamic nucleus. This projects to the dorsal insular cortex that is involved in a variety of interceptive modalities such as thermoception, visceral sensations, thirst, and hunger (reviewed in Refs. 71, 805, 954). As shown by functional positron emission tomography (fPET), induction of itch by intradermal histamine injections and histamine prick induced coactivation of the anterior cingulate cortex, supplementary motor area, and inferior parietal lobe, predominantly in the left hemisphere (183, 544). This considerable coactivation of motor areas explains the common observation of itch being essentially linked to a desire to scratch. The multiple activated sites in the brain after itch induction argue against the existence of a single itch center and reflect the multidimensionality of itch. Moreover, a broad overlap of activated brain areas is evident for pain and itch (221). However, subtle differences in the activation pattern between itch and pain have been described. For example, in contrast to pain, itch is characterized by a lack of secondary somatosensory cortex activation on the parietal operculum and by a left hemispheric dominance (221). Of note, recently observed that the periaqueductal gray matter (PAG) was observed only to be activated when painful and pruritic stimuli were simultaneously applied. This activation was combined with reduced activity of the anterior cingulate, dorsolateral prefrontal cortex, and parietal cortex, suggesting that the PAG might be involved in the central inhibition of itch by pain (544).

Although pain and itch are different entities, a close relation exists between them. Both pain and itch can be reduced by soft rubbing which activates fast-conducting low-threshold fibers (117). However, the most characteristic response to itching is the scratch reflex: a more or less voluntary, often subconscious motoric activity, to counteract the itch by slightly painful stimuli. This itch reduction is based on a spinal antagonism between pain and itch-processing neurons (724). Thus itch appears to be under tonic inhibitory control of pain-related signals (21, 293, 724, 805). Indeed, itch and pain share the use of many neurophysiological tools and processing centers, and come along with similar autonomous skin reactions. Also, chronic pain and central sensitization to itch appear to be neurophysiologically closely related neurophysiological phenomena (71).

Neurophysiological recordings from the cat spinal cord support the concept of dedicated pruritoceptive neurons existing independently of pain fibers. Craig and Andrew (21) characterized a specialized class of mechanically insensitive, histamine-sensitive dorsal horn neurons projecting to the thalamus. Thus the combination of dedicated peripheral and central neurons with a unique response pattern to pruritogenic mediators and anatomically distinct projections to the thalamus provides the basis for a specialized neuronal itch pathway. The important role of the cutaneous PNS and CNS in the transmission of pain is reviewed elsewhere (397, 592).

C. Neuroanatomy and Neurophysiology of Autonomic Nerves

The anatomy of cutaneous autonomic nerves has been intensively reviewed by Brain (106). Autonomic nerve fibers in the skin almost completely derive from sympathetic (cholinergic) and, in the face, rarely parasympathetic (also cholinergic) neurons. Although very effective, they constitute only a minority of cutaneous nerve fibers compared with sensory nerves. Also in contrast to sensory nerve fibers, the distribution of autonomic nerves is restricted to the dermis, innervating blood vessels, arteriovenous anastomoses, lymphatic vessels, erector pili muscles, eccrine glands, apocrine glands, and hair follicles (902) (Figs. 1 and 2) (see sect. III*B* for details). Thus cutaneous autonomic nerves are involved in the regulation of blood circulation, lymphatic function, and the regulation of skin appendages (sweat glands, apocrine glands, hair follicles).

In general, cholinergic autonomic activity tends to be more pronounced in the dermis, although acetylcholine can be also produced by keratinocytes (155–157, 461). In addition, muscarinic and nicotinergic acetylcholine receptor expression has been described on keratinocytes in vivo and in vitro (285, 287–289).

Postganglionic autonomic nerves in the skin predominantly generate acetylcholine, although recent observations revealed an additional role for neuropeptides within the skin autonomic nervous system. Thus, in addition to classical neurotransmitters, autonomic nerves also release neuropeptides such as neuropeptide Y (NPY), galanin, calcitonin gene-related peptide (CGRP), or vasoactive intestinal polypeptide (VIP) (341, 536). Moreover, they generate neuromodulators such as tyrosine hydroxylase, which can be also used as a marker for autonomic nerves in the skin. Accordingly, immunoreactivity for NPY and atrial natriuretic peptide (ANP) (845) is only observed in autonomic nerve fibers, which differentiates them from sensory nerve fibers (73) (Table 2).

The cutaneous autonomic nervous system plays a crucial part in regulating sweat gland function and thereby body temperature homeostasis. The role of acetylcholine as an important regulator of sweating is well explored (721–723) (see also Table 2). In contrast, the exact role of autonomic nerve-derived neuropeptides such as CGRP, VIP, and galanin, for example, is only poorly understood (160, 341, 558, 574). For example, CGRP and VIP seem to interact in the regulation of the

TABLE 2. *Selected neuromediators and their functions in cutaneous biology*

Mediator	Receptors	Sources, Receptors Expressed by	Comments
Acetylcholine	Nicotinergic (nAChR) and muscarinergic (mAchR) acetylcholine receptors	Autonomic cholinergic nerves, keratinocytes, lymphocytes, melanocytes	Mediates itch in atopic dermatitis patients. mAChR3 is probably involved in itch. Regulates keratinocyte proliferation, adhesion, migration, and differentiation. Inhibits NFκB transcription; inhibits release of TNF-α, IL-1β.
Adenosine triphosphate (ATP)	Purinergic P2 receptors (seven ionotropic P2XRs or eight metabotropic P2YRs). HMEC-1 express P2X4, P2X5, P2X7, P2Y2, and P2Y11 receptors, and weakly P2X1 and P2X3		Involved in pain transmission and neurogenic inflammation. Induces release of IL-6, IL-8, MCP-1, Gro-α from HMEC-1 cells. Increases expression of ICAM-1 in HMEC-1. Increases leukocyte recruitment and adhesion to EC.
Calcitonin gene-related peptide (CGRP) (and adrenomedullin, ADM)	CGRP receptor = calcitonin-like receptor/receptor activity modifying protein 1 (CL-R/RAMP1) ADM-receptor = CL-R/RAMP2 or CL-R/RAMP3	CGRP: sensory nerve fibers CGRP receptor: keratinocytes	Pain transmission (central but not periphery), prolongation of itch latency following SP injection (inhibitory effect on itching). Sensitization of sensory nerve endings. Increase of CGRP fibers in itchy skin diseases. CGRP stimulates adhesion of leukocytes and monocytes to endothelial cells. Vasodilatation and relaxation of arterioles; CGRP but not ADM potentiates edema in venules, ADM less potent than CGRP as a direct vasodilator. ADM but not CGRP potentiates neutrophil accumulation induced by IL-1β. CGRP stimulates TNF-α release from mast cells. Potential role on angiogenesis and keratinocyte migration. With adrenomedullin, CGRP inhibits progression of sepsis.
Catecholamines	Adrenergic receptors (AR): α_{1a}, α_{1b}, α_{2A}, α_{2B}, α_{2C}, α_{2D}, β_1, β_2 and β_3 AR	Released by nerve fibers, keratinocytes, melanocytes. Receptors by natural killer cells, monocytes, T cells Inducible by T cells, B cells	Suppresses IL-12 production and increases IL-10 release in DCs. Inactivates NFκB. Augments T-cell production. Inhibits TNF-α release from monocytes. Modulates keratinocyte differentiation. Regulates melanogenesis.
Corticotropin releasing hormone (CRH) (see also opioids and proopiomelanocortin)	CRH-R1 and -R2	CRH-R1: keratinocytes, mast cells CRH-R2: bone marrow mast cells	Release of histamine, cytokines, TNF-α, VEGF from mast cells. CRH-like immunoreactivity on sensory nerves (rat). CRH-R1 downregulation upon stress and infection. CRH-R2 mRNA induced by IL-4 in mast cells. High expression of CRH-R1 in urticaria and lichen simplex. CRH proliferative in fibroblasts and antiproliferative in keratinocytes. Stimulates corticosterone production in fibroblasts. Downregulates IL-18 in human keratinocytes. CRH regulates pigmentation, produces analgesia in thermal pain models.
Endocannabinoids	Cannabinoid receptors (CB1, CB2)	Released by nerves, T cells, macrophages Receptors on nerves, mast cells, macrophages, keratinocytes, skin appendages	Antipruritic in the periphery; antinociceptive and antihyperalgesic in rats and humans. Activate the TRPV1 pathway, inhibit cytokines during innate and adaptive immune responses, downregulate release of IL-1, TNF-α and CXCL8. Suppress TH1-cell activity and increase TH2-cell activity; decreases production of IFN-γ and IL-12 and expression of IL-12R; increases IL-4 production. LPS stimulates release of cannabinoids from macrophages and DCs; macrophages increase production of endocannabinoids in response to LPS; protective effect during endotoxemia and sepsis. Attracts human eosinophils, B cells, DCs, increased in HIV. CB2 reduces cutaneous edema; CB1-dependent reduction of transglutaminase, PKC, and AP-1 in keratinocytes; CB2-dependent release of β-endorphin from keratinocytes. Anti-inflammatory and antipruritic in the periphery, downregulates IL-1 and TNF-α, and upregulates IL-10.

TABLE 2—*Continued*

Mediator	Receptors	Sources, Receptors Expressed by	Comments
Endothelin (ET)	Endothelin receptors (ET_A, ET_B)	Nerves, endothelium, mast cells, fibroblasts, melanocytes	Burning itch. Degraded by chymase via ET_A, receptor activation thereby regulating inflammation and probably itch. ET-1 induced TNF-α, and IL-6 production by mast cells. Tissue remodeling and fibrogenesis by inducing synthesis of collagen I. ET_B mediates upregulation of melanoma cell adhesion molecule.
Interleukin-31	IL-31R (heterodimer)	Keratinocytes, sensory nerves	IL-31 released during skin inflammation by T cells and macrophages, induce release of inflammatory mediators from keratinocytes, induces itching.
Kallikreins, proteases	Partly by proteinase-activated receptors (PARs, tryptic enzymes)	PAR1: keratinocytes, endothelial cells, mast cells, platelets PAR2: keratinocytes, endothelial cells, mast cells, nerves PAR4: T cells, mast cells, (macrophages?)	Tryptase attenuates the vasodilator activity of calcitonin gene-related peptide. Chymase induced angiogenesis, clearance of cytokines. Microbial agents induce prekallikrein synthesis; hK5 and hK7 are inhibited by LEKT1. pH affects serine protease activity in the epidermis. Kallikreins may be involved in systemic sclerosis. PAR1: platetet regulation; induces proliferation in keratinocytes; MMP-1 activates PAR1. PAR2: massive itch behavior in mice overexpressing epidermal kallikrein-7. Potential role of other kallikreins. Chymase degrades pruritic and antipruritic peptides. Tryptase induces inflammation and itch by a neurogenic mechanism via PAR2. Microbial proteases may induce itch and inflammation via PAR2 PAR4?
Kinins	Bradykinin receptors (B1, B2)	Endothelial cells, immunocytes, keratinocytes, sensory nerves fibers	Bradykinin induces pain over pruritus. Modulates nociception. B2 receptor antagonists reduce itch. Bradykinin induces MAP kinase phosphorylation in keratinocytes.
Leukotriene B_4	Leukotriene B_4 receptor	Sensory nerves fibers, keratinocytes	Leukotriene B_4 induces itch and is also involved in the substance P- and nociceptin-mediated induction of itch. Mast cell-derived LTB_4 modulates T-cell proliferation and activation.
Neurokinin A (NKA) Substance P (SP) Hemokinin-1 (HK-1)	Tachykinin (neurokinin) receptor-1, −2, −3	Sensory nerve fibers, dermal microvascular endothelial cells, keratinocytes, B cells	SP: upregulation ICAM-1 and VCAM-1, priming of mast cells. Release of TNF-α, histamine, leukotriene B_4, and prostaglandins from mast cells (agents involved in pruritus and burning). SP involved in central pain transmission. Protachykinin contributes to delta-opioid receptor-mediated pain processing. HK-1: expressed by T cells and macrophages; involved in B-cell development and stimulates IFN-γ production in T cells. NKA: upregulation of keratinocyte nerve growth factor expression.
Endovanilloids (heat, acidosis, eicosanoids, histamine, bradykinin, extracellular ATP, prostaglandins, various neurotrophins)	Activation of vanilloid receptor-1 (TRPV1) Sensitization of TRPV1 via activation of specific receptors	TRPV1 is expressed on sensory neurons, mast cells, epidermal and hair follicle keratinocytes, Langerhans cells, smooth muscle, sebocytes	TRPV1: short-term TRPV1 activation: pain and itch induction, depletes neuropeptides from sensory neurons. Long-term antipruritic effect of TRPV1 agonists (e.g., capsaicin): suspend interplay between sensory neurons and mast cells. Affects epidermal and hair follicle proliferation, differentiation, apoptosis, and cytokine release. Increased expression in epidermal keratinocytes of prurigo nodularis patients; induces neurogenic inflammation, sensitized by PAR2. TRPV2: expressed by medium- to large-diameter sensory neurons, induced by noxious heat; upregulation contributes to peripheral sensitization during inflammation and is responsible for pain hypersensitivity to noxious high-temperature stimuli. TRPV3: induced by innocuous (warm) temperatures, expressed by keratinocytes. Impaired thermosensation in mice lacking TRPV3; interaction with P2X receptors? TRPV4: activated by heat (25°C), by cell swelling, and PLA_2; expressed by sensory neurons, sympathetic nerves, sweat glands, keratinocytes, hair cells, Merkel cells, murine aorta endothelial cells; involved in pain-related behavior; transduction of osmotic and mechanical stimuli. TRPM8: activated by temperature (below 27°C), menthol, eucalyptol; expressed by small-diameter DRGs; no colocalization with neuropeptides. TRPA1: activated at 17°C, expressed exclusively in DRGs, sensitive to icilin (AG-3-5), insensitive to menthol, eucalyptol; colocalizes with TRPV1, SP, and CGRP.

TABLE 2—*Continued*

Mediator	Receptors	Sources, Receptors Expressed by	Comments
Galanin	Galanin receptor (1–3) (GalR1–3)	Gal: nerve terminals and fibers of the dermis and basal layer of epidermis GalR: nerves fibers	Mice overexpressing galanin show moderate heat hypoalgesia, reduced spinal sensitization, and reduced development of neuropathic painlike behavior. Increases membrane excitability and enhances Ca^{2+} currents in acutely dissociated rat DRGs.
Histamine	Histamine receptors (H1R, H4R)	Sensory nerve fibers, endothelial cells, T cells	In humans, histamine induces itch by stimulating specific sensory fibers, whereas H1 and and H2 antagonists reduce itch in numerous clinical trials. In mice, H3 antagonists induce scratching behavior, whereas H1 and H4 antagonists effectively suppress pruritus. Induces also plasma extravasation and vasodilatation; communicates with T cells via histamine receptors.
Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins (NT-3, NT-4)	Specific receptors trk A: NGF; trk B: NT-4, BDNF; Trk C: NT-3	Keratinocytes, mast cells, fibroblasts, eosinophils	NGF levels enhanced in atopic dermatitis (AD). Induces tryptase release from mast cells. Inducible by histamine. trk A: enhanced in keratinocytes during inflammation. NT-4: enhanced in AD and induces sprouting. BDNF: increases eosinophil chemotaxis levels in AD and inhibits apoptosis. Neurotrophins sensitize receptive nerve endings and upregulate neuronal neuropeptides and TRPV1. NGF is upregulated during inflammation, stimulates mast cells and released by them. NGF increases number of mast cells, induces proliferation and differentiation of B cells, and stimulates neuronal cells. NT-3 inhibits inflammatory hyperalgesia in rats. During inflammation, upregulated BDNF accelerates tactile recovery in rats.
Neuropeptide Y (NPY)	Neuropeptide Y receptor-1 and -2 (Y1, Y2)	Sensory nerves, keratinocytes	Inhibition of adenylyl cyclase, regulating blood flow, reflex vasoconstriction.
Opioids	μ-, κ-, δ-Opioid receptors (partly receptor-independent cell activation)	Sensory nerves, keratinocytes, T cells, B cells	Antipruritic effect of μ-opioid antagonists (central effect) and κ-opioid agonists (spinal cord level). Opioid agonists do not provoke itch upon injection or intradermal application. μ-Opioid receptor upregulation in atopic dermatitis. Keratinocyte-derived β-endorphin induces peripheral analgesia. T cells express various opioid receptors: opioids induce T-cell chemotaxis. Inhibits B-cell IgG production via IL-6 modulation. Absence of classical opioid receptors on human mononuclear cells.
Pituitary adenylate cyclase activating polypeptide (PACAP)	PAC1R, PAC2R, PAC3R (and splice variants); also binds to VPAC1R and VPAC2R	Sensory and autonomic nerves, T cells, macrophages, keratinocytes, dermal microvascular endothelial cells, Merkel cells	In vivo: potent vasodilatator; involved in flush, pain, neurodegeneration. PACAP enhanced in lesions of psoriasis patients. Enhances animal survival during sepsis. Downregulates capacity of APCs for antigen presentation: inhibiting the induction of contact hypersensitivity by reducing murine LCs. In vitro: induces release of histamine from mast cells; downregulates release of IL-2, IL-6, TNF-α from T cells and macrophages. Early inflammation: drives T cells into an anti-inflammatory response. Late inflammation: stimulates T-cell proliferation and differentiation into Th2 helper cells.
Proopimelanocortins (POMC gene) (endorphins, enkephalins, dynorphins, MSH, ACTH, β-lipotrophin) (see also CRH, opioids)	Opioid receptors, MC-R, ACTH-R, CRH-R	Melanocytes, keratinocytes, adnexal epithelial cells, endothelial cells, Langerhans cells, mast cells, fibroblasts, monocytes, and macrophages	Upon cleavage by prohormone convertase (PC1, 2) POMC-derived peptides mediate a variety of processes in skin function (please refer to the specific section of POMC peptides).
Prostaglandins	Prostanoid (P) receptors (DP, EP, IP)	Sensory nerve fibers, keratinocytes	PGE_2 induces pain over itch in humans but not mice. PGD_2 reduces IgE-mediated scratching in mice. PGE_2 is a vasodilator and may potentiate edema in the skin; DP1 impedes TNF-α-induced migration of human LCs, inhibits the chemotactic responses of human LCs to chemokines, induces IL-10 production. Mice lacking DP2 and EP2 show reduced flushing in mice. PGE_2 and PGI_2 upregulate ICAM-1 expression in human gingival fibroblasts; COX-2 inhibitor (NS-398) elevates IgE and a systemic TH2 response to antigen in mice.

TABLE 2—*Continued*

Mediator	Receptors	Sources, Receptors Expressed by	Comments
Somatostatin (SST) (1–14, 1–28)	sst receptors 1–5	Skin: Merkel cells, sweat glands, Langerhans cells, keratinocytes, fibroblasts, macrophages	In atopic skin, the expression of SST diasappeared. SST has inhibitory effects on T-cell proliferation. SST-2 is found macrophages in sarcoidosis. Antiproliferative on keratinocytes. Anti-inflammatory: downregulation of proinflammatory cytokines. Sst receptors upregulated in melanoma.
Secretoneurin	Not known	Sensory nerve fibers	Secretoneurin triggers monocyte migration, modulates neutrophil activity, and stimulates endothelial migration.
Vasoactive intestinal polypeptide (VIP)	VPAC1R, VPAC2R	Sensory and autonomic nerves, T cells, macrophages, keratinocytes, dermal microvascular endothelial cells, Merkel cells, smooth muscle cells	Anti-inflammatory in mammals and humans; induces NO synthesis; upregulates IL-10 in DCs; downregulates TLR4 expression and TLR4-mediated chemokine generation; downregulates IL-1, TNF-α, and MCP-1; antiapoptotic in Th2 cells; induces vasodilatation; supports migration of keratinocytes; regulation of blood vessel function. Inhibits delayed-type hypersensitivity and prevents from graft-versus-host disease in vivo. Enhances outcome of animal survival during sepsis. Induces pruritus and increases blood flow in human skin. Poor effect on plasma extravasation.

cholinergic sympathetic innervation of rat sweat glands (467). ANP may serve a similar role in the skin as in the kidneys. It regulates water and electrolyte balance in various organs, and its immunoreactivity is found predominantly in sympathetic cholinergic fibers around sweat glands (reviewed in Ref. 455). Since released VIP is capable of triggering sweat secretion in glandular eccrine sweat glands through a cAMP-dependent activation mechanism (844), it is tempting to propose a similar role for VIP as for ANP. However, good controlled studies in animals and humans are still lacking. Thus, in addition to acetylcholine, neuropeptides released by autonomic nerves may be crucially involved in the regulation of sweat gland function and probably dysfunction of sweat secretion (hyperhydrosis, hypohydrosis) based on uncontrolled sympathetic innervation, as it has been described in diseases such as congenital sensory neuropathy type IV, progressive segmental hypohydrosis, diabetic neuropathy, syringomyely, lepra, and after sympatectomy (307, 370, 650, 663).

Adult human sweat gland innervation, however, is not only cholinergic but coexpresses all of the proteins required for full noradrenergic function as well, including tyrosine hydroxylase, aromatic amino acid decarboxylase, dopamine β-hydroxylase, and the vesicular monoamine transporter VMAT2. Thus cholinergic/noradrenergic cotransmission is apparently a unique feature of the primate autonomic sympathetic nervous system. Furthermore, sympathetic neurons innervating specifically the cutaneous arteriovenous anastomoses (Hoyer-Grosser organs) in humans also possess a full cholinergic/noradrenergic cophenotype (928).

Autonomic nerve fibers are also crucially involved in the regulation of vascular effects in the skin. Sympathetic nerve fibers release norepinephrine and/or NPY to innervate arterioles, arteriovenous anastomoses, and venous sinusoids which results in vasoconstriction, whereas parasympathetic nerves mediate vasodilatation through activation of venous sinusoides by the release of ACh and VIP/peptide histidine methionine (PHM) (5, 108, 407, 916). The occurrence of VIP within intradermal nerves is variable in different studies and appears to be species specific. The distribution of VIP, however, along with its ability to stimulate adenylate cyclase activity in vascular and glandular cells suggests an important role of VIP for the regulation of blood vessels as well as sweat gland function within the autonomic cutaneous nervous system (467, 743) (Table 2).

Effective heat exchange in the skin is controlled by terminal capillary loops that are regulated by shunt vessels, the arteriovenous anastomoses. Small arteries and arterioles as well as the arteriovenous anastomoses are richly supplied with noradrenergic nerves (316). The control of skin blood flow is maintained through two branches of the sympathic nervous system: a vasoconstrictor system and an active vasodilator system of unknown neurotransmitter. Previous studies suggest that this system is cholinergic and involves a cotransmitter, possibly VIP (52). Cholinergic sympathic nerves are also known to stimulate eccrine sweat glands via muscarinic receptors (106), whereas higher concentrations of acetylcholine induce an axon-reflex flare mediated via nicotinic receptors. In the vasoconstrictor system, the transmitter appears to be norepinephrine along with one or more cotransmitters.

The best characterized sympathic cotransmitters that participate in the regulation of blood flow include ATP (131) and NPY (818). NPY and norepinephrine were re-

cently shown to be the major mediators of the reflex cutaneous vasoconstrictor response to body cooling. NPY acted mainly via the Y1 receptor and to a less extent via the Y2 receptor (160). Moreover, NPY was suggested to contribute to the nonnoradrenergic mechanism of reflex vasoconstriction (818). However, the role of NPY in the response to local cooling is subtle compared with its more pronounced role in the reflex responses to whole body cooling (391).

Local cooling stimulates cold-sensitive receptors that, in addition to conveying the thermal information centrally, also act on sympathetic vasoconstrictor nerves locally to stimulate release of norepinephrine to cause the initial vasoconstriction. This vasoconstriction masks a nonneuronal vasodilator response that may be present upon a more intense cooling (391, 632). Skin without intact sensory or autonomic function exhibits this vasodilator response, which is replaced by nonneurogenic vasoconstriction. The mechanisms for the nonneurogenic vasodilator and vasoconstrictor components of the response to direct cooling are unknown. In comparison, direct local warming of skin leads to vasodilation that involves nitric oxide (NO) and sensory nerves (424, 817) (Fig. 2, Table 2).

Both autonomic as well as sensory nerve fibers are reportedly involved in hair follicle cycling and inflammation (reviewed in Ref. 620). However, recent studies in denervated skin of C57BL/6 mice demonstrated that intact hair follicle innervation was not essential for anagen induction and development, although it had a minor modulatory role in depilation-induced hair growth (521). Various studies on the role of acetylcholinergic and adrenergic transmitters in cutaneous biology have been extensively reviewed elsewhere (680, 713, 769, 920, 933) (see also sect. IV, Fig. 3).

III. BIOLOGICAL ACTIVITIES OF THE CUTANEOUS SENSORY NERVOUS SYSTEM

A. Towards a Modern Concept of Neurogenic Inflammation

Stricker (823), and later Bayliss (47), described for the first time that cutaneous vasodilatation was achieved after stimulation of cut dorsal nerve roots. As described above, the identification and characterization of polymodal and chemosensitive small afferent nerve fibers (C and Aδ nociceptors) provided evidence that cutaneous nerves may participate in skin inflammation. Thus neurogenic inflammation was found to be predominantly or exclusively mediated by afferent chemosensitive C nociceptors. The role of Aδ fibers in skin inflammation and pain is still not understood. According to the "classical" concept of neurogenic inflammation, the mediators of the antidromic axon reflex were released from different specialized afferent nerve terminals and not from the sensory nerves themselves (48, 119, 479) (Fig. 3).

This classical concept could be extensively completed by using a vanilloid compound, capsaicin, which directly stimulated the sensory nerve. Capsaicin, the pungent ingredient of "hot" chili peppers has become an important topic for understanding neurogenic inflammation, pain, and pruritus in various tissues including the

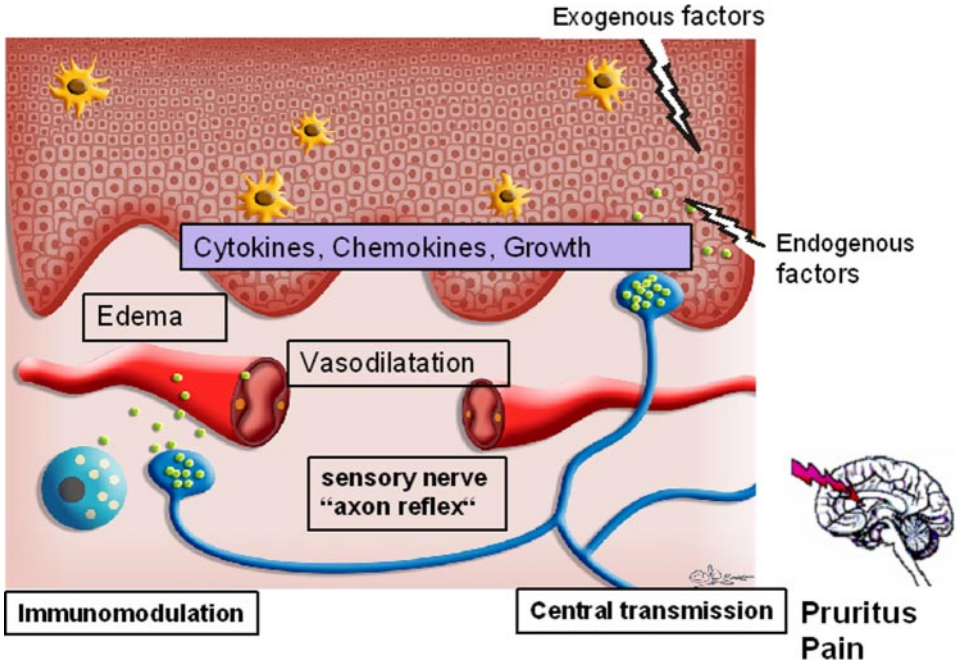

FIG. 3. Modern aspects of cutaneous neurogenic inflammation. Exogenous (heat, scratching, irritants, allergens, ultraviolet light, microbiological agents) or endogenous (pH changes, cytokines, kinins, histamine, proteases, neurotransmitters, hormones, "stress") trigger factors may directly or indirectly stimulate nerve endings from primary afferent neurons. Stimuli are transmitted to the central nervous system, thereby affecting regions involved in pruritus, pain, somatosensory reactions (scratching) and probably emotional responses. Second, peripheral nerve endings stimulate neighboring afferent nerve fibers in the dermis and epidermis, a process known as "axon reflex." Stimulated release of neuropeptides results in vascular responses ("triple response of Lewis," erythema by vasodilatation, and edema by plasma extravasation), modulation of immunocyte function (e.g., mediator release from mast cells), and regulation of mediator release (cytokines, chemokines, growth factors) from keratinocytes and Langerhans cells.

skin. Capsaicin applied to the skin produces a burning sensation that is abolished by cold and intensified by heat. Jancso et al. (372), and later Szolcsanyi (839), initially observed the phenomenon of "capsaicin desensitization," a long-lasting chemoanalgesia and impairment in thermoregulation against heat. The pharmacological properties of capsaicin in sensory-innervated tissues like the skin led to the hypothesis of an existing "capsaicin receptor" on polymodal C fibers (reviewed in Refs. 372–374, 839, 841). Hence, this view fostered a new way of understanding sensory nerves as peptidergic regulators of inflammation. Thus the capsaicin-sensitive sensory nervous system serves as a "dual afferent-efferent" sensor whereby initiation of afferent signals and neuropeptide release are coupled at the same nerve endings. A new highlight was the discovery of the "capsaicin receptor," a six-transmembrane temperature-gated ion channel, now defined as "transient receptor potential vanilloid 1" (TRPV1).

Although electric stimulation of capsaicin-insensitive afferent nerve fibers may result in pain or pruritus, it does not lead to inflammatory responses in normal skin underlining the specific role of capsaicin-chemosensitive C fibers in this process (840). The cutaneous flare response can be inhibited by prior treatment of the skin with topical capsaicin over several days because sensory nerves are depleted of neuropeptides (58, 144, 252). Thus capsaicin-sensitive C fibers and to a lesser extent Aδ fibers are not only capable of transporting impulses to the CNS (orthodromic signal) but also releasing neuropeptides (antidromic signal) that result in inflammatory activities within the skin.

Neuropeptides released from cutaneous nerves act on target cells via a paracrine, juxtacrine, or endocrine pathway. These target cells express specific neuropeptide receptors that are appropriately coupled to an intracellular signal transduction pathway or ion channels, which, when activated, may result in activation of biological responses such as erythema, edema, hyperthermia, and pruritus. Because of their anatomical association to cutaneous nerves, mast cells and their released products appear to play an important role in mediating neuronal antidromic responses in the skin, although their precise role in cutaneous inflammation is not known. Because afferent sensory neurons express specific receptors for neuropeptides, prostaglandins, histamine, neurotrophins, opioids, proteases, cytokines, and immunoglobulins (19), an interactive communication network between sensory nerves and immune cells likely exists during cutaneous inflammation (103, 787). Finally, cell-associated neuropeptide-degrading peptidases such as neutral endopeptidase (NEP), angiotensin converting enzyme (ACE), or endothelin converting enzyme (ECE)-1 have been shown to modulate neurogenic inflammation by limiting the effects of neuropeptides in the skin (739, 740, 804). Thus the interaction between sensory nerves releasing neuropeptides, target cells with functional receptors, and neuropeptide-degrading peptidases is critical for determining neurogenic inflammation (Fig. 1). The roles of NO (457, 833), purinergic receptors (127, 133, 342, 733, 748), prostaglandin (102, 163, 400, 879) and leukotriene receptors (102, 701, 971), and voltage-gated ion channels (302, 318, 531, 553, 900) in the interaction with the skin nerval system have been extensively reviewed.

B. Cutaneous Neuropeptides and Neuropeptide Receptor Biology

With a few exceptions, neuropeptides consist of a group of small peptides of 4 or more than 40 amino acids that exert their effects by interacting with members of a superfamily of G protein-coupled receptors with seven transmembrane domains (GPCRs). Immunohistochemistry studies in the skin have demonstrated the presence of multiple neuropeptides, neurotransmitters, and neurohormones in sensory nerves including substance P (SP), neurokinin A (NKA) (180), neurotensin, CGRP, VIP, pituitary adenylate cyclase activating polypeptide (PACAP) (549, 809), peptide histidine-isoleucinamide (PHI), NPY (380), somatostatin (SST) (76), β-endorphin, enkephalin, galanin, dynorphin, secretoneurin, ACh, epinephrine, norepinephrine (NE), α- or γ-melanocyte-stimulating hormone (MSH) (386, 497), and corticotropin-releasing hormone (CRH) (64, 240, 743, 768, 769, 845). Colocalization of distinct neuropeptides can be observed in different tissues including the skin. For instance, sensory nerve fibers are immunoreactive for SP and CGRP (761), SP and PACAP (549), or CGRP and SST (76). However, the factors that determine the relative concentration of these neuropeptides in different nerve fibers of the skin are not well understood, although distinct regulatory functions of neuropeptide-neuropeptide interactions have been observed (33, 418).

Various neuropeptides are produced and released by a subpopulation of unmyelinated afferent neurons (C fibers) defined as C-polymodal nociceptors, which, as mentioned above, represent ~70% of all cutaneous C fibers in the skin. To a lesser extent, small myelinated Aδ fibers and autonomic nerve fibers are also capable of releasing a number of neuropeptides that also act on neuronal and nonneuronal target cells. Despite similarities in structure, a large variety of neuropeptides have been identified; some of them have been generated by posttranslational modifications of a precursor molecule. In addition, recently, cutaneous cells themselves such as keratinocytes, microvascular endothelial cells, Merkel cells, fibroblasts, or leukocytes were found to be capable of releasing neuropeptides under physiological circumstances (477, 919).

Dermal blood vessels are not only highly innervated by sensory and autonomic nerve fibers, but they also

synthesize certain neuropeptides after activation and express receptors for neuropeptides, which suggests that a complex autocrine and paracrine neuroendocrine system may exist in the skin. Arterial sections of arteriovenous anastomoses, precapillary sphincters of metarterioles, arteries, and capillaries appear to be the most intensely innervated regions. Although sensory nerves are important for vasodilatation, neuropeptides from sympathetic neurons such as NPY mediate vasoconstriction supporting an important role for neuropeptides in vascular regulation. Both endothelial cells and smooth muscle cells respond to neuronal modulation during processes such as inflammation, cellular immune responses, neovascularization, and wound healing (for catecholamines, see Ref. 4).

This section summarizes our current knowledge about the role of crucial neuromediators, neurotrophins, and neurotransmitters as well as their receptors in modulating skin physiology and pathophysiology. The role of certain neuromediators in the skin has been comprehensively reviewed and is thus only mentioned under certain aspects (39, 137, 176, 177, 211, 437, 440, 667, 769, 770, 884, 920).

1. Tachykinins and neurokinin receptors

Tachykinins are small peptides consisting of 10–13 amino acids with a conserved COOH-terminal sequence (FXGLM) and different ionic charges at the NH_2 terminus, the latter of which is crucial for receptor binding and affinity. In mammals, SP, NKA, and NKB, and the NKA-variants neuropeptide K (NP-K) and neuropeptide γ (NP-γ) are encoded by two distinct genes. Specific mRNA splice variants of the preprotachykinin A gene encodes SP, NKA, substance K, and NP-γ, whereas the preprotachykinin B gene encodes NKB (reviewed in Refs. 130, 510, 734).

Only recently, the novel SP-like peptide hemokinin-1 (HK-1) that is encoded by the preprotachykinin C gene was identified in mouse B cells and shown to be a potentially important regulator of B-cell development (959, 960). In humans, a homologous preprotachykinin C polypeptide was found to be expressed in a variety of tissues with strong signals detected in the skin. Binding and functional analysis indicated that human HK-1 peptides were nearly identical to SP in their overall activity profile on the three NK receptors with the most potent affinity for the NK1 receptor. The results indicate that preprotachykinin C encodes another high-affinity ligand of the NK1 receptor which may play an important role in mediating some of the physiological roles previously assigned to the NK1 receptor (460).

The expression of preprotachykinin A mRNA, SP, and NKA in cells of neuronal and nonneuronal origin have been shown to be regulated by certain proinflammatory mediators [interleukin (IL)-1, lipopolysaccharide (LPS)] and neurotrophins [nerve growth factor (NGF)], respectively (91, 255, 893). In human skin, a dense innervation with tachykinin-immunoreactive nerves in the upper and lower dermis, as well as epithelium, supports the capacity for these neuropeptides to participate in sensory nerve transmission as well as interaction with epidermal and dermal target cells (228, 230).

In the skin, tachykinin-immunoreactive sensory nerves are often associated with dermal blood vessels, mast cells, hair follicles, or epidermal cells (671). Increased epidermal SP-immunoreactive nerve fibers have been observed in certain inflammatory human skin diseases such as psoriasis, atopic dermatitis, and contact dermatitis (reviewed in Refs. 540, 811). Moreover, several immune cells are capable of generating SP induced by stress, inflammation, or infection (569, 570, 596). For example, SP appears to be involved in keratinocyte/antigen-presenting cell interactions during chronic stress (569), T-cell regulation (607), natural killer cell activation (485), innate host defense (116), human immunodeficiency virus (HIV)-associated psoriasis (338, 570), wound healing (189), murine hair follicle apoptosis (636), genital herpes infection (836), and immunosurveillance during experimentally induced tumor growth (murine melanoma) (509). SP may be also involved in inflammation and host responses of the CNS (511) as well as transmitting sensory signals (neurogenic inflammation, pain, pruritus) to the CNS (reviewed in Refs. 622, 805). In addition, in a murine disease model, the NK1 receptor was recently shown to play an important role in the development of airway inflammation and hyperresponsiveness (889).

SP released by sensory neurons after noxious stimuli provokes erythema, edema, and pruritus. Tumor necrosis factor (TNF)-α release from human skin may be induced by SP via activation of the mitogen-activated protein kinase (MAPK) pathway (599). SP is also capable of mediating secretion of histamine and TNF-α from mast cells, which results in vasodilatation via activation of H1 receptors on vascular smooth muscle cells (23, 170). SP also directly induces the release of cytokines such as TNF-α, IL-1β, IL-2, and IL-6 from rat leukocyte subpopulations (190). SP may also induce the release of leukotriene B_4, and prostaglandin D_2 from skin mast cells, suggesting that granulocyte infiltration mediated by LTB_4 may be generated in response to SP (257). Another study (762) recently showed that acute immobilization stress triggers skin mast cell degranulation via SP, CRH, and neurotensin. This finding agrees with observations from other studies that found in vitro activation of murine DRG neurons by CGRP-mediated mucosal mast cell degranulation during acute immobilization stress in experimental murine cutaneous leishmaniasis (689). This effect was reduced when animals were treated neonatally with capsaicin to deplete their sensory neurons of their neuropeptides. Thus stress via release of certain neuropeptides may trigger degran-

ulation of skin mast cells and influence certain inflammatory skin responses and pruritus by release of SP, CGRP, and other neuropeptides (860).

Neuropeptides are capable of activating dermal microvascular endothelial cells by binding high-affinity receptors. For example, SP can directly modulate proinflammatory biological activities of human dermal microvascular endothelial cells (HDMEC) (936), such as upregulation of cell adhesion molecules such as intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 (656, 657). In addition, intracutaneous SP and CGRP rapidly induce cutaneous neutrophilic and eosinophilic infiltration that is accompanied by translocation of P-selectin to luminal endothelial cell membranes and expression of E-selectin (775). SP can also induce a concentration-dependent induction of IL-8 in HDMEC (452, 736). Taken together, these results suggest an important direct effect for neuropeptides in modulating proinflammatory activities of endothelial cells in the skin.

SP and NKA are also capable of activating keratinocytes resulting in a number of proinflammatory cytokines (527, 619). For example, production of the proinflammatory cytokines IL-1α, IL-1β, and IL-8 as well as the IL-1 receptor antagonist in murine and human keratinocytes is upregulated by SP (118, 780, 903). SP is capable of directly activating both murine and normal human keratinocytes to induce IL-1 in a dose-dependent manner (23, 780, 831), suggesting a regulatory role of sensory nerve fibers that extend directly into the epidermis where they come in direct contact with both keratinocytes and Langerhans cells (181, 348). Interestingly, this effect can be inhibited by NK receptor antagonists. Recent findings suggest that SP may induce NFκB activation and interferon-induced protein of 10-kDa production in synergy with interferon-γ via neurokinin-1 receptor on keratinocytes. SP induction of murine keratinocyte PAM 212 IL-1 production is mediated by the neurokinin 2 receptor (NK-2R) (129, 738).

These effects of SP may be mediated via phospholipase C activation, intracellular Ca^{2+} signal, and reactive oxygen intermediates (415). Furthermore, during wound healing, SP may promote the healing process by affecting the expression of both epidermal growth factor and epidermal growth factor receptor in the granulation tissues as demonstrated in a rat model (464). In addition, keratinocyte NGF is induced by sensory nerve-derived neuropeptides such as SP and NKA (129). This direct effect of the neurosensory system on keratinocyte NGF production may have important consequences for the maintenance and regeneration of cutaneous nerves in normal skin and during inflammation and wound healing. Keratinocytes themselves have been reported to express preprotachykinin A mRNA and SP, indicating an autocrine induction of SP in human keratinocytes (37). Finally, SP may modulate cutaneous inflammatory responses by upregulation of cell adhesion molecule expression on keratinocytes (903).

In cultured normal human fibroblasts a moderate amount of preprotachykinin A was found, which was significantly upregulated by exogenous SP. Also the expression of NEP was increased in fibroblasts stimulated with SP (38). Accordingly, SP was found to promote human fibroblast chemotaxis in a dose-dependent manner (406). Moreover, SP fragments (from endopeptidase degradation) [SP-(1–4) and SP-(3–11)] were used to find that the chemoattractant potency of these fragments was due to the COOH terminus of SP which is known to be active on neurokinin receptors (904, 906). The involvement of the NK1R in the chemotactic response to SP was also indicated by fibroblast migration toward optimal concentration of a selective NK1R agonist but not a NK2R agonist, suggesting a NK1R-mediated role of SP on human fibroblast chemotaxis (406). SP also augments fibrogenic cytokine-induced fibroblast proliferation (417) and works synergistically with IL-1 and platelet-derived growth factor to stimulate the proliferation of bone marrow fibroblasts (661). SP was also shown to enhance dose-dependently the proliferation of fibroblasts derived from human normal skin. After 48 h of culture with SP, fibroblasts expressed significantly more transforming growth factor (TGF)-β1 mRNA than unstimulated fibroblasts. The effects of SP on both fibroblast proliferation and TGF-β1 mRNA expression could be antagonized by a selective NK1R antagonist, suggesting that SP may play an important role in phenotype changes of fibroblast proliferation. In cultured rheumatoid fibroblast-like synoviocytes, SP enhances cytokine-induced VCAM-1 expression in a dose-dependent manner, probably via NK1R activation. This finding favors a role for SP in the pathophysiology of autoimmune diseases such as rheumatoid arthritis (465) and is supported by observations in human skin fibroblasts (614, 969). Furthermore, SP may be linked to wound healing via fibroblast activity. The cell surface enzyme NEP degrades SP, thereby regulating its biologic actions. In fact, it was shown that elevated NEP activity in the skin and chronic ulcers of subjects with diabetes combined with peripheral neuropathy may contribute to deficient neuroinflammatory signaling and impaired wound healing (25). The selective nonpeptide antagonist for NK1R [(+/−)CP 96,345] diminished the effects elicited by the NK1 selective agonist [Sar9]-SP-sulfone ([Sar9]-SP) on cellular transduction mechanisms in stable, cultured, human skin fibroblasts. The exposure of the cells to the agonist [Sar9]-SP produced an early increase in inositol 1,4,5-trisphosphate (IP_3) levels and a later rise in cellular inositol 1-phosphate (IP_1) content, whereas cAMP level was not significantly modified. The $[Ca^{2+}]_i$ mobilization in response to the NK1 agonist produced a rapid increase in the intracellular Ca^{2+} level, indicating a concentration-dependent increase in both the ratio and the number of

cells responding to [Sar9]-SP. These results clearly demonstrate that NK1R stimulation results in cellular transduction mechanisms in human skin fibroblasts. In human lung fibroblasts neuropeptides were shown to modulate fibroblast activity, particularly with respect to proliferation and chemotaxis. NKA and SP stimulated human lung fibroblast proliferation, whereas VIP and CGRP had no such effect. NKA alone stimulated fibroblast chemotaxis, and phosphoramidon, a NEP inhibitor, enhanced fibroblast proliferation in a dose-dependent manner. Thus neuropeptides have the potential to cause activation of mesenchymal cells, which is potentially regulated, at least in part, by NEP activity (320). In summary, tachykinins may modulate inflammation in the skin by a direct effect of neurokinins on several target cells in normal and inflamed skin.

SP, NKA, and NKB bind with different affinities to neurokinin receptors (NKRs) that belong to the G protein-coupled receptor family (251, 669). Mast cells, fibroblasts, keratinocytes, Merkel cells, endothelial cells, and Langerhans cells (23, 241, 283, 339, 614, 780, 794) express functional NKR, albeit G proteins of mast cells can be additionally activated by SP in a non-receptor-mediated fashion (125, 126, 559, 560). To date, three neurokinin receptors and one splice variant have been cloned and characterized, all of which differ in their binding affinity to SP, NKA, and NKB.

Binding of SP, NKA, and NKB by NK receptors is primarily determined by the NH_2-terminal portion of the tachykinin peptide, whereas the COOH terminus is essential for receptor desensitization (339, 904, 906). Several studies have identified transcriptional gene regulators mediated by SP, including NFκB, NFAT (482, 655), cAMP responsive elements (CRE), and activator protein-1 (AP-1) (158). However, there seem to be species-specific differences in neurokinin receptor expression. For example, NK2R expression is significantly higher in murine keratinocytes (780), whereas NK1R is preferentially expressed on human keratinocytes (654). In summary, tachykinins may modulate inflammation in the skin by a direct effect of neurokinins on several target cells in normal and inflamed skin.

Previous studies using the tachykinin NK1R antagonist SR140333 indicate that cutaneous edema can be mediated by NK1Rs and is independent of histamine effects (613). This finding is supported by experiments using NK1R knockout mice, which showed that intradermally injected SP, NK1R agonists (GR-73632), and the mast cell-degranulating agent compound 48/80 induced dose-dependent cutaneous edema in wild-type mice that was lacking in knockout mice. Capsaicin and exogenous tachykinins induced edema formation, which was reduced by a histamine (H1) receptor antagonist (mepyramine), indicating that tachykinins are capable of mediating cutaneous edema formation via NK1R activities. Additionally, edema induced by tachykinins may be partially affected by NK1Rs on mast cells, since capsaicin- and SP-induced edema formation was reduced by the histamine H(1) antagonist mepyramine (140). Moreover, in vivo studies using neurokinin-1 receptor knockout mice have demonstrated that NK1R agonists are involved in modulating neutrophil accumulation in the inflamed, but not normal cutaneous microvasculature (740). A similar result was observed in a tissue culture model of human skin in which SP induced a dose-dependent edema, vasodilation, and extravasation of lymphocytes and mast cells through the microvascular wall and the release of proinflammatory mediators IL-1 and TNF-α in vitro (113). SP may directly cause vasodilatation on vascular endothelial cells via NK1R (100). Recent studies show that SP-induced vasodilatation is partly mediated by NO, whereas CGRP-induced vasodilatation appears to be NO independent (436).

In a rat model, it was shown that tachykinin receptor antagonists exerted inhibitory effects on thermally induced inflammatory reactions (487) through both NK1R and NK2R. Thus SP and probably NKA contribute to inflammatory reactions after thermal injury and increase both local edema as well as the nociceptive transmission at the spinal cord level. Studies using a specific NK1R antagonist and a specific CGRP receptor antagonist [CGRP-(8–37)] in rats support the role that SP, NKA, and CGRP play in mediating antidromic vasodilatation in the skin (309, 487).

Whether neutrophil accumulation occurs after neuropeptide-mediated inflammatory responses is not known. Some authors failed to detect a role for the NK1R in cutaneous neutrophil recruitment (645), but others have shown that the number of neutrophils is reduced in NK1R knockout mice during contact hypersensitivity (CHS) (735) or SP inhibition (634).

In summary, various important target cells in the skin that participate in cutaneous inflammation express appropriate tachykinin receptors for released neurokinins by sensory fibers or immunocompetent cells, respectively. These findings strongly indicate that SP- and NKA-mediated activation of tachykinin receptors contribute to inflammatory reactions and that the tachykinin receptor antagonists can reduce both the local inflammatory response and the nociceptive transmission at the spinal cord level.

2. VIP

VIP is a 28-amino acid peptide that derived from a precursor mRNA (preproVIP) that also encodes histidine-methionine (PHM) (187, 280, 699). In the skin, VIP-like immunoreactivity was detected in nerve fibers associated with dermal vessels; glands such as sweat, apocrine, and Meibominan glands; hair follicles; and Merkel cells. VIP

immunoreactivity was less abundant than SP immunoreactivity in the epidermal layer (322, 743). VIP-staining fibers can be also found in close anatomical connection to mast cells (299, 323, 571). VIP immunoreactivity can be detected in various immunocompetent cells in different species, and VIP is an important molecule within the "neuroimmunological network" (186, 199, 269, 272, 652) (Table 2).

In the skin, functional studies with VIP found that this peptide may also mediate vasodilatation (52, 938) and proliferation (312, 943) as well as induce migration of keratinocytes that may be important in wound healing (943) and psoriasis (154, 379, 408, 572, 615, 641, 832).

Moreover, VIP reportedly regulates sweat production and accumulation of intracellular cAMP (229, 230, 703). However, VIP was not only identified as a physiologically active neuropeptide and neurotransmitter, but is further involved in neurogenic inflammation possibly through histamine release from mast cells and bradykinin-induced edema (17, 922). VIP may also play a role during infection. For example, antibodies against VIP were found in patients with HIV and were more prevalent in asymptomatic carriers, i.e., their titer correlated with disease progression (894).

VIP-induced stimulation of histamine release may lead to subsequent vasodilatation and increased plasma extravasation, suggesting a direct effect of VIP on the regulation of blood vessel function (52, 774). For example, VIP may cause direct vasodilatation by inducing NO synthesis, which results in vasorelaxation (270). The migration of monocytes from blood vessels into the inflammatory tissue is also increased by VIP. However, the molecular mechanisms and the receptors involved in this process are still unclear. Although VIP1-R mRNA was detected almost exclusively in endothelial cells with radioactive in situ hybridization, the VIP2-R could be seen in endothelial as well as smooth muscle cells (887). Immunohistochemical studies with affinity-purified polyclonal antibodies confirm this observation in human skin tissue (759).

It is well established that VIP is involved in neuroimmunomodulation (199). This cytokine-like peptide exerts a broad spectrum of anti-inflammatory effects in mammals including humans (272). In murine T cells, VIP has the capacity to modulate CD4+CD25+ Foxp3-expressing regulatory T cells in vivo. Application of VIP into T-cell receptor transgenic mice resulted in the expansion of T cells that inhibited the responder T-cell proliferation, increased the level of CD4+CD25+ Treg cells, inhibited delayed-type hypersensitivity in TCR-Tg hosts, and prevented graft-versus-host disease in vivo (192).

In human T cells and T-cell lines, VIP modulates IL-2 secretion (296) and induces Th2 responses by promoting Th2 differentiation and survival. Interestingly, VIP modulates the upregulation of granzyme B, FasL, and perforin in Th2 but not Th1 cells, thereby regulating Th2 cell survival by preventing apoptosis (749). VIP seems to be directly involved in regulating dendritic cell (DC)/T-cell interactions. VIP induced the generation of tolerogenic DCs, thereby producing CD4 and CD8 Treg cells (271). Moreover, VIP induced upregulation of IL-10 in human DCs in vitro. Thus VIP may be involved in regulating Th1 cell responses and may be an effective compound for the treatment of autoimmune diseases. Finally, VIP inhibits antigen-induced apoptosis of mature T lymphocytes by suppressing Fas ligand expression (193). Together, these results strongly support a regulatory immunosuppressive role of VIP on T cells and DCs by downregulating TNF-α, IL-1, IL-6, and NO (115, 196), while stimulating the release of IL-10, for example.

In macrophages, VIP and PACAP protect mice from lethal endotoxemia through the inhibition of TNF-α and IL-6, suggesting a protective role of both neuropeptides in innate immunity (197) by downregulating TNF-α production (200). VIP and PACAP inhibited TNF-α activation via regulating NFκB and cAMP response element-binding protein (CREB)/c-*jun*, a cAMP-dependent pathway that increases CREB binding versus c-*jun* binding to the cAMP response element-binding site (CRE), and a cAMP-independent pathway that inhibits binding of NFκB (194, 198, 473). VIP is also involved in modulating innate immunity by downregulating TLR4 expression and TLR4-mediated chemokine generation (CCL2, CXCL8) (306).

Animal studies clearly indicate a role for VIP in modulating inflammatory diseases in vivo. For example, VIP regulates CD4+CD25+ Treg cells during experimental autoimmune encephalomyelitis and T cells as well as DCs during contact hypersensitivity and arthritis (191, 441, 892). In neutrophils and macrophages, VIP regulates the outcome of animal survival during sepsis (195, 197, 515). Together, these findings suggest an important protective role of VIP in T cell-mediated diseases as well as innate immunity and host defense.

3. PACAP

PACAP is a relatively new member of the VIP/secretin peptide family (542). Two forms can be distinguished, PACAP-38 and a truncated product PACAP-27, both of which are derived from a 176 precursor protein (19.5 kDa) by posttranslational cleavage (349). The mature peptide has a molecular mass of ~5 kDa. PACAP has been localized in nerve fibers of different tissues, including skin (Table 2), from a number of species as well as in lymphoid tissues of the rat and lymphocytes from the peripheral blood (reviewed in Ref. 27).

PACAP is present in sensory and autonomic nerve fibers of dorsal root ganglia, the spinal cord, and the adrenal glands, suggesting involvement in sensory and nociceptive pathways (223, 549). Moreover, PACAP-im-

munoreactive fibers are sensitive to capsaicin (549). In various organs of rodents and humans, PACAP displays neuroprotective, regenerative, and immunomodulatory functions. In SCID mice, CD4+ T cells appear to induce PACAP gene expression, suggesting a regulatory role of immune cells on PACAP-induced immunomodulation and nerve regeneration (28).

In the skin, PACAP was detected in sensory nerve fibers (597, 809) coexisting with VIP, SP, or CGRP, respectively, all of which may play an important role in inflammatory skin diseases like psoriasis, urticaria, or atopic dermatitis (643) (reviewed in Ref. 24). In rat skin epithelium, PACAP has been detected especially within highly innervated structures like the tongue and the nose (549).

The distribution of PACAP-38 (597, 809) and the presence of the high-affinity PACAP1 receptor (PAC1R) (809) was described in normal and inflamed human skin. The concentration of PACAP-38 appears to be enhanced in lesional skin of psoriasis patients, indicating that this neuropeptide has a role in the pathophysiology of this skin disease (809). Moreover, the peptide level was significantly lower in nonlesional psoriatic skin than in lesional psoriatic skin, but was about twice as much as in normal human skin. Interestingly, immunoreactivity was significantly increased at the dermal-epidermal border in psoriasis (809). Further immunoreactivity was localized between connective tissue, around hair follicles, and close to sweat glands of normal skin. In contrast, no significant increase of positive nerve fibers was observed around blood vessels. PACAP appears to be involved in cutaneous inflammation, e.g., by releasing histamine from mast cells (597).

Several observations support the idea that PACAP modulates inflammatory responses in the skin: PACAP-27 produces a long-lasting depression of a C fiber-evoked flexion reflex in rats (961), indicating that PACAP plays an essential role in nociceptive transmission in the skin (394). Moreover, PACAP is a potent vasodilatator and edema potentiator in rabbit skin (921) and mediates plasma extravasation in rat skin (142, 730). From these data one may speculate that C fibers release PACAP in response to activation by a currently unknown stimulus that leads to vasodilatation and extravasation. Additionally, in a rodent model, VPAC1 and VPAC2 receptors play an important role in pressure-induced vasodilatation, suggesting a protective feature against applied pressure (247).

Recent findings suggest that PACAP stimulates histamine release from murine mast cells via direct stimulation of G proteins (730, 746). Using mast cell-deficient mice with or without transplantation of mast cells, Schmidt-Choudhury et al. (732) were able to show that intracutaneously injected PACAP produces a long-lasting, partially mast cell-dependent edema compared with mast cell-deficient mice, supporting a close interaction of PACAP-positive nerve fibers and mast cell regulation of murine skin. In humans, intravenous injection of PACAP leads to a long-lasting flush phenomenon. Thus PACAP may have a vasodilatory function in human skin that may also contribute to neurogenic inflammation.

Recent observations indicate that PACAP is also involved in immunomodulation. In murine T cells, PACAP can downregulate IL-2 and inhibit IL-10 expression (512) and IL-6 production; in murine peritoneal macrophages, PACAP can inhibit secretion (513, 514). These findings were recently confirmed in a study in which PACAP inhibited the induction of contact hypersensitivity by reducing murine LC antigen-presenting cell (primary and XS106 cell line) properties (441). Additionally, PACAP inhibits the LPS/granulocyte-macrophage colony stimulating factor (GM-CSF)-induced stimulation of IL-1β and augments IL-10, presumably by modulation of cytokine production (442). VIP and PACAP both inhibit the LPS-stimulated production of TNF-α via VPAC1R and activation of the adenylate cyclase system in vitro and in vivo, suggesting a protective role for VIP and PACAP regulating the release of TNF-α during inflammation (194, 200). Finally, PACAP and VIP via VPAC1R inhibit TNF-α production at a transcriptional level in murine macrophages through two pathways, a cAMP-dependent pathway that increases CREB binding versus c-*jun* binding to the CRE, and a cAMP-independent pathway that inhibits binding of NFκB (194, 198, 473). Finally, VIP and PACAP inhibit antigen-induced apoptosis of mature T lymphocytes by inhibiting Fas ligand expression (193). These results strongly support a regulatory role of PACAP and VIP for proinflammatory molecules such as TNF-α, IL-1, IL-6, and NO (115, 196).

In this context, Delgado and co-workers (192, 193) recently showed that PACAP itself also regulates human T-cell function. Human DCs express receptors for PACAP and VIP, predominantly VPAC1R. Interestingly, PACAP exhibits a diverse role of action depending on the status of the inflammatory response. During an ongoing inflammation, PACAP drives T cells into an anti-inflammatory response (downregulation of proinflammatory cytokines), whereas in an ongoing immune response, PACAP upregulates CD86 expression on DCs thereby stimulating T-cell proliferation and differentiation into Th2 helper cells (201).

In summary, these results suggest an important role of PACAP during inflammation and neurotransmission within the neurocutaneous network.

4. VIP/ PACAP receptor family

So far, three different VIP/PACAP receptors (PVRs) with additional splicing products have been cloned (reviewed in Ref. 27) that were recently defined as PAC1-R (=PACAP1-R), VPAC1-R (=PACAP2-R = VIP1-R), and VPAC2-R (=PACAP3-R = VIP2-R). Since VIP and PACAP

are capable of binding identical receptors in the same tissue but with different affinities (PAC1-R = high-affinity receptor for PACAP; VPAC1-R = low-affinity receptor for PACAP and high-affinity receptor for VIP; VPAC2-R = low-affinity receptor for VIP and PACAP), a differential fine-tuned interaction between these two peptides can be suggested. The PACAP/VIP receptor family can be found in several species. In humans, all three receptor subtypes can be detected in different peripheral organs, and the human high-affinity PAC1-R consists of at least five splice variants (648). PAC1-R, for example, has a significantly higher affinity for PACAP than VIP (207). Immunohistochemical and biochemical studies support a regulatory role of PVRs in skin inflammation. Binding sites for VIP have been identified on a variety of cells including sweat glands (329), keratinocytes (847), and immune cells (139, 199). VPAC1-R was detected in endothelial cells, VPAC1-R and VPAC2-R in smooth muscle cells, and VPAC1-R in keratinocytes (291, 832). RT-PCR experiments further give evidence of the occurrence of a PAC1-R in normal as well as in inflamed human skin, suggesting a receptor-mediated function of PACAP in human skin tissues, although the receptor subtypes have not yet been localized (299).

All three subtypes of the PACAP/VIP receptor family are coupled to G_s proteins, which mediate the activation of adenylate cyclase (135, 706). In addition, the PAC1-R is also associated with G_q and G_i proteins (647, 783). Activation leads to a PACAP-mediated recruitment of secondary messengers like diacylglycerol, IP_3, and $[Ca^{2+}]_i$, as well as activation of potassium channels. PACAP also stimulates proliferation in different cell lines that was comparable to growth factors like EGF (707, 710, 711). This mitogenic effect was mediated through the PAC1-R and was associated with MAPK activation (p42/p44). PACAP also induces activation of transcription factor complexes such as AP-1 and c-*fos*. Interestingly, low doses of PACAP induce proliferation, whereas high doses initiate differentiation and induce apoptosis in pancreas epithelial cells. However, the underlying molecular mechanisms of this observation are unknown (710, 711).

By means of differential-display RT-PCR in different PACAP-treated tumor cell lines, Schafer et al. (709) identified a new PACAP-responsive early response gene (p22/PRG1) that encodes a 160-amino acid polypeptide with a molecular mass of 22 kDa (p22). p22/PRG1 appears to play a role in cell cycle regulation, and the promoter region contains binding sites for transcription factors that are involved in growth control and inflammation, respectively, such as NFκB, AP1, myc/max, or p53 (705, 710). With an electromobility shift assay and CAT-reporter gene assays, p22/PRG1 was shown to be a specific target for the tumor suppressor gene p53 (708), which suggests an important role for PACAP in growth regulation and apoptosis.

The migration of monocytes from blood vessels into the inflammatory tissue is also enhanced by VIP. However, the molecular mechanisms and the receptors involved in this process are still unclear. Although VIP1-R mRNA was detected almost exclusively in endothelial cells with radioactive in situ hybridization, the VIP2-R could be seen in endothelial and smooth muscle cells (887). Immunohistochemical studies with affinity-purified polyclonal antibodies confirm this observation in human skin tissue (759).

Recent knowledge indicates that PAC1-R and VPACRs are prominent in the immune system and regulate many aspects of neuroimmunomodulation. In murine T cells, PACAP downregulates IL-2 and inhibits IL-10 expression (512), and IL-6 production and secretion is inhibited in PACAP-treated murine peritoneal macrophages (268, 513, 514, 909). VIP and PACAP both inhibit the LPS-stimulated production of TNF-α via VPAC1-R, and activation of the adenylate cyclase system in vitro and in vivo, suggesting a protective role for VIP and PACAP regulating the release of TNF-α during inflammation (197, 200). VIP and PACAP inhibited antigen-induced apoptosis of mature T lymphocytes by inhibiting Fas-ligand expression (193). Interestingly, a deletion variant of the murine VPAC2-R (delta-367–380) has been identified which produced decreased cAMP levels, IL-2 release, and ameliorated chemotaxis of T cells (296).

In murine macrophages, PACAP and VIP via VPAC1-R inhibit TNF-α production at a transcriptional level through two pathways, a cAMP-dependent pathway that increases CREB binding versus c-*jun* binding to the CRE, and a cAMP-independent pathway that inhibits binding of NFκB (198). These results strongly support a regulatory protective role of PACAP and VIP during inflammation such as downregulating TNF-α, IL-1, and NO. Vice versa, VIP/PACAP receptors (VPACRs) as well as PAC1R mediate anti-inflammatory stimuli like upregulation of IL-10.

The PAC1-R is also involved in regulating innate immunity (515). During experimentally induced murine septic shock, PACAP attenuates LPS-mediated upregulation of IL-6. Moreover, PAC1R mediates the recruitment of murine neutrophils by modulating ICAM-1, VCAM-1 expression, and fibrinogen synthesis (515).

In summary, these results suggest an important role of PACAP during inflammation and neurotransmission within the neurocutaneous network.

5. CGRP

The calcitonin gene-related peptides CGRP1 and CGRP2 (346, 800) are 37-amino acid neuropeptides that differ by 3 amino acids and are members of a peptide family that includes calcitonin adrenomedullin and amylin (799). CGRP1α, and CGRP1β belong to one gene family since both are generated from the same gene locus by

RNA splicing (15, 16). CGRP1β consists of 37 amino acids that are translated from a 1.2-kb mRNA. CGRP1β differs from CGRP1α only by exchange of one amino acid (K^{35} to E^{35}). Interestingly, CGRP1α is preferentially expressed by sensory neurons, whereas CGRP1β is predominantly found in enteric neurons (819, 820).

CGRP is one of the most prominent neuropeptides of the skin and is often colocalized with either SP or SST (261). CGRP-immunoreactive nerves are often associated with mast cells (95), Merkel cells (240), melanocytes (317), keratinocytes, and Langerhans cells (LC) (31, 348), which are stimulated under inflammatory conditions (34). Additionally, CGRP immunoreactivity was detected in association with smooth muscle cells and blood vessels (454, 917). For example, CGRP alone can increase keratinocyte proliferation (317) and regulate cytokine production in human keratinocytes. CGRP and SP also upregulated IL-8 mRNA expression but not IL-8 production in HaCaT cells (434).

CGRP has been shown to modulate immune responses and inflammation in vitro and in vivo. In general, CGRP predominantly mediates anti-inflammatory and neurotrophic effects (939) (Table 2). For example, systemic administration of CGRP significantly reduced neutrophil accumulation (260). CGRP also reduced inflammatory responses in vivo in a mouse ear edema induced by croton oil as well as an acetic acid-induced peritonitis model of the rat (168). Both CGRP as well as adrenomedullin exert potent vasoactive effects (853). Phagocytosis by peritoneal macrophages was increased in vitro by CGRPα, indicating a protective role of macrophage function for this neuropeptide (363). However, CGRP also stimulated adhesion of human neutrophils and monocytes (U937) to HUVEC (830) and dermal microvascular endothelial cells (736), also indicating a proinflammatory role in acute early inflammation. In addition, CGRP potentiated the accumulation of neutrophils and edema formation induced by IL-1 (124, 830) or induced mast cells to release TNF-α which resulted in inflammatory effects on surrounding skin cells (580). An excellent overview of receptor-mediated vascular activities of CGRP has been recently published (105).

Recent studies show that neuropeptides directly effect cytokine production and expression of cell adhesion molecules in HDMEC. HDMEC are a potentially important target cell population in cutaneous neurogenic inflammation. Cutaneous sensory fibers are found in close contact with dermal microvascular endothelial cells. Recent studies indicate that cutaneous neuropeptides are capable of inducing IL-8 production in HDMEC (452, 736).

CGRP is one of the most potent vasodilatory mediators on small and large vessels (107, 109, 111, 376) and potentiates microvascular permeability and edema formation caused by SP or NKA, although the effects of CGRP seem to be more long-lasting. NO is released from dermal microvascular endothelial cells by CGRP, indicating a direct effect of this peptide on endothelial cells although CGRP-induced vasodilatation could not be blocked by an NO synthesis inhibitor (436). Furthermore, direct activation of CGRP receptors on endothelial cells and/or smooth muscle cells are discussed as well as mast cell activation (365). Ca^{2+}-activated or ATP-sensitive K^+ channels may be also responsible for this mechanism (345). CGRP and endothelin are colocalized in endothelial cells, suggesting autoregulatory mechanisms for blood flow (611).

Intravenous injection of CGRP increased vasodilation and skin temperature in rats in a dose-dependent manner. CGRP had a greater vasodilatatory effect than VIP or SP (590). The increase was significantly greater in rats that had been ovariectomized than in sham-operated rats and was inhibited by pretreatment with human CGRP-(8–37), a CGRP receptor antagonist, in a dose-dependent manner (589). In addition, ovariectomy increased the number of CGRP receptors in mesenteric arteries. These results suggest that the low concentration of plasma CGRP due to ovarian hormone deficiency may induce the increase in the number of CGRP receptors due to upregulation. Therefore, the increased number of CGRP receptors may be responsible for potentiation of exogenous αCGRP-induced increase in skin temperature in ovariectomized rats. The mechanism underlying the hot flashes observed in menopausal women may also, in part, involve the upregulation of CGRP receptors following ovarian hormone deficiency (589).

CGRP was shown to increase both cell number and DNA synthesis, whereas NKA, NPY, and VIP were ineffective. Furthermore, ^{125}I-labeled CGRP was shown to bind to human umbilical vein endothelial cells (HUVECs), suggesting the existence of specific CGRP receptors. CGRP also stimulated cAMP formation, indicating that CGRP may act as a local factor stimulating proliferation of endothelial cells, which is associated with cAMP formation (736). Thus CGRP may be important for the formation of new vessels during physiological and pathophysiological events such as inflammation and wound healing (311).

CGRP may be regulated by UV-mediated responses because irradiation of the skin decreased CGRP mRNA expression in dorsal root ganglia (264). Moderate noxious heat induces calcium-dependent CGRP release from nerve fibers that can be facilitated by bradykinin and by PKC activation (427). The same study showed that heating the skin induced a temperature-dependent release of CGRP that was absent in calcium-free solution. Thus noxious heating induces an axon-reflex response in the skin, which is due to the release of neuropeptides such as CGRP from polymodal nociceptors.

In human skin, CGRP-immunoreactive nerve fibers are associated with epidermal melanocytes. CGRP also induces melanocyte proliferation by upregulating melano-

genesis and enhances melanocyte dendricity by inducing keratinocyte-derived melanotrophic factors (873). Interestingly, skin exposed to CGRP showed increases in melanocyte number, epidermal melanin content, melanosome number, and degree of melanization. CGRP alone had no significant effect, whereas the addition of medium conditioned by CGRP-stimulated keratinocytes (CGRP-KCM) induced melanogenesis, suggesting that keratinocytes produce melanotrophic factors after stimulation, which indicates a modulatory role of CGRP for epidermal melanocyte function.

6. CGRP-like receptors

Historically, CGRP receptors have been divided into two classes, $CGRP_1$ and $CGRP_2$. $CGRP_1$ receptors are more sensitive than $CGRP_2$ receptors to the peptide antagonist $CGRP_{8-37}$ (203, 658), whereas the linear CGRP analogs [$Cys(ACM)^{2,7}$]- and [$Cys(Et)^{2,7}$]-αCGRP are more potent agonists at $CGRP_2$ receptors than at $CGRP_1$ (203, 222, 554). The orphan receptor, calcitonin-like receptor (CL-R), has been shown to require a single transmembrane domain protein, termed receptor activity modifying protein (RAMP) to function as a CGRP receptor (529; for review, see Ref. 651). So far, three RAMPs (RAMP1, -2, and -3) have been characterized. The RAMPs share a common topological organization but less than 30% sequence identity (529). CL-R/RAMP2 and CL-R/RAMP3 act as adrenomedullin receptor, whereas coupled with CL-R/RAMP1 function as a CGRP1 receptor (254, 973). Thus the expression of RAMPs may determine the specificity of CL-R for adrenomedullin or CGRP, respectively. The fact that RAMPs are differently regulated during different disease states indicates a regulatory role for RAMPs and CL-R in tissue pathophysiology (566).

Stimulation with CGRP leads to an increase in intracellular cAMP via coupling to the heterotrimeric G protein G_s and phosphoinositide turnover (317, 469). CGRP activates guanylate cyclase and phospholipase C as well as calcium and potassium channels (292, 469). Moreover, CGRP activates phospholipase C-β1 via $G\alpha_{q/11}$ during calcium mobilization (217). Recently, CL-R was detected in arteriolar smooth muscle and venular endothelium of human hairy skin. This finding is consistent with CGRP's putative role in neurogenic inflammation and suggests novel targets for CGRP such as capillary endothelium, hair follicles, and sweat glands (314).

A novel protein was recently identified as a CGRP-receptor component protein (CGRP-RCP) (494). This intracellular peripheral membrane protein couples the CRLR to the cellular signal transduction pathway, and its expression correlates with potency of CGRP in various tissues (236, 568). Thus a functional CRLR may consist of at least three proteins: the receptor, the chaperone protein (RAMP), and the RCP that couples the receptor and facilitates the downstream signal transduction. However, the precise role of this receptor complex in cutaneous inflammation remains to be determined.

7. SST and receptors

SST was originally described as a neurotransmitter that has a wide spectrum of biological activities in the CNS and several peripheral organs (274, 275). Endogenous SST occurs in two biologically active forms: either a 14- or 28-amino acid peptide. SST has been detected in the CNS, PNS, lung, and gastrointestinal tract (672). SST expression appears to be regulated via PKA-dependent phosphorylation of CREB. In the skin, SST-14 immunoreactivity has been demonstrated in Merkel cells (241), associated with sweat glands (381, 384), in keratinocytes, and in LCs. In the dermal layer, SST-14 specific antisera stained dendritic cells as well as SST-positive nerves (259, 541). Interestingly, the SST expression was diminished in lesional atopic skin but not in controls (642) (Table 2).

SST is described as an inhibitor of exocrine and endocrine secretion from a variety of tissues including pancreas, gastrointestinal tract, and the CNS and PNS (670). Additionally, SST is regarded as a predominantly antiproliferative molecule that has cancer-inhibiting properties that are mediated by tyrosine phosphatases (134, 483) and inhibitory effects on proliferation of T lymphocytes (624). SST released from sensory nerves may have an immunosuppressive role in some basophil-dependent hypersensitivity reactions, because SST inhibited the release of histamine and leukotriene D_4 by human basophils challenged with anti-human myeloma IgE (267). The inhibitory effects of SST may not be generalized, because SST stimulated histamine release of human skin mast cells (164). Further support for the immunomodulatory function of SST comes from studies showing that concanavalin A-induced proliferation and IgG synthesis by murine lymphocytes expressing SST receptors is inhibited by physiological concentrations of SST. SST and the SST analog angiopeptin decreased the adhesion for monocytes to unstimulated and IL-1-stimulated endothelial cells by a cAMP-dependent mechanism that does not involve ICAM-1, implying that SST may attenuate recruitment of distinct leukocyte subpopulations during the initial phase of inflammation (476). There is evidence for the participation of SST in the pathophysiology of atopic dermatitis and mastocytosis (382, 387, 642).

8. Somatostatin receptors (sst)

To date, five different types of somatostatin receptors (sst_{1-5}) have been cloned and characterized (51, 481, 673). The different receptor types can be subdivided in two classes of either low affinity (sst-1, sst-4) or intermediate to high affinity for short synthetic SST analogs such as octreotide (sst-2, sst-3, sst-5). All receptors are func-

tionally coupled to G proteins, bind SST-14 as well as SST-28 with high affinity, and mediate a pertussis toxin-sensitive inhibition of adenylate cyclase (121). In general, the antiproliferative properties of SST may be mediated by sst-1 and sst-2 and involve the activation of tyrosine phosphatases (488). In cultured fibroblasts, assays with biotinylated SST and radioligand binding (259) have shown that subtypes 2 or 3 of SST receptors are present on human normal dermal fibroblasts and that SST-14 exerts a dose-dependent effect on DNA synthesis and cell proliferation.

Recently, ten Bokum and co-workers (856, 857) have demonstrated the immunohistochemical localization of somatostatin receptors in inflammatory lesions of patients suffering from rheumatoid arthritis, sarcoidosis, and Wegener's granulomatosis. Sst2A was observed in epithelioid cells, multinucleated giant cells, and a subset of CD68+ macrophages (856). Moreover, treatment with octreotide resulted in clinical improvement in one of two treated patients with sarcoid granulomas (856) or systemic sclerosis (206), suggesting a role for analogs in treating granulomatous diseases. Finally, sst2a has also been detected recently in rat trigeminal ganglia (362).

9. *Opioids, proopiomelanocortin (POMC) peptides, and receptors*

Opioids, which are cultivated from opium plants, have been known about for at least 5,000 years. The oldest known opioid, opium, was mentioned as a "plant of joy" in ancient Egyptian literature, and the famous ancient Persian physician Avicenna used it to treat cough, anemia, and diarrhea. Opium later became famous for its addictiveness. One of the alkaloids within the opium, morphine, has long been established as a potent analgesic and antinociceptive drug. Endogenous opioids were more recently discovered in invertebrates and vertebrates (490) and found to be important messengers as hormones and neurotransmitters (801, 803) (Table 2).

Opioids are peptidergic neurotransmitters especially known for their potent analgesic capacity. More than 20 opioid peptides are currently known. They can be divided into three classes: the endorphins, enkephalins, and dynorphins (Table 2). The active forms are liberated after proteolytic cleavage of the inactive prepropeptide (preproopiomelanocortin, preproenkephalin A, preprodynorphin). They are generated from different genes and exhibit marked variations in skin physiology and pathophysiology (104, 797).

Opioid receptors are the primary sites of actions for opiates and endogenous opioid peptides. The receptors are classified into three subtypes, μ, δ, and κ. Activation of opioid receptors generally inhibits neuronal excitability through inhibition of voltage-dependent Ca^{2+} channels, adenylyl cyclase, and activation of K^+ channels (704). Opioid receptors are characterized by a widespread distribution in the central and peripheral nervous system. In primary afferent neurons, for example, the release of SP is tightly regulated by opioid receptors. Double in situ hybridization showed that μ-opioid receptor mRNA was located to 90% in preprotachykinin-containing DRGs, indicating that opioids interact in the transmission of nociceptive function (537).

10. *POMC and endorphin peptides*

POMC is a 31-kDa precursor protein that is intracellularly generated by posttranslational processing. The POMC gene includes several bioactive peptides (endorphins) such as adrenocorticotrophic hormone (ACTH); β-lipotropin; α-, β-, and γ-MSH; β-endorphin, and Met-enkephalin. Posttranslational processing of a POMC prohormone generates up to seven different POMC peptides after cleavage by prohormone convertase 1 and 2 (PC1, -2). These enzymes appear crucial for the tissue specificity of POMC-derived peptides because PC1 and PC2 expression show tissue-specific regulation. PC1 generates ACTH and β-lipotropin, whereas PC2 cleaves POMC into α-MSH and β-endorphin, respectively. Posttranslational acetylation and amidation may also modify the biological activity of POMC derivates (3; for a recent review, see Ref. 660).

POMC peptides, originally discovered as pituitary hormones, have been detected in various tissues including the skin and are expressed by melanocytes, keratinocytes, adnexal epithelial cells, microvascular endothelial cells, Langerhans cells, mast cells, and fibroblasts as well as by immune cells such as monocytes and macrophages (496). The hair follicle therefore seems to generate the whole armada of mediators generated by the hypophysial-adrenal (HPA) axis such as β-endorphin, MSH, ACTH, CRH, their receptors (μ-opioid receptor, MC-R, ACTH-R, CRH-R), and enzymes regulating POMC peptide function like PC1 and PC2 (367).

11. *β-Endorphin*

β-Endorphin is involved in a variety of physiological and pathophysiological conditions of the skin (764). For example, it can be stimulated in human keratinocytes via activation of the μ-opioid receptor (μOR) by UV radiation. In human melanocytes, β-endorphin has melanogenic, mitogenic, and dendritogenic effects in vitro and expresses μOR (421). Accordingly, human hair follicle melanocytes also express β-endorphin and μOR, especially in glycoprotein-100-positive cells, suggesting a role during hair growth in an autocrine fashion. Thus β-endorphin may be involved in pigmentation and hair growth.

Recent findings indicate that β-endorphin also has a role in cutaneous neurogenic inflammation and analgesia. Endothelin-1 (ET-1) activates β-endorphin release from

human keratinocytes, which in turn mediates analgesia via activation of the endothelin-B receptor (ET_B) and the linked rectifying potassium channels (GIRKs) on primary afferent neurons (428). Similarly, cannabinoids seem to regulate the release of β-endorphin from keratinocytes, thereby modulating nociception in the skin. Recently, Ibrahim et al. (361) showed that selective agonists of the cannabinoid-2 (CB-2) receptor (AM1241) stimulated the release of β-endorphin from keratinocytes and rat skin tissue in a dose-dependent manner. β-Endorphin release from keratinocytes was prevented in vitro and in vivo by antagonists to the CB-2 receptor or when CB-2 receptor-deficient mice were used. Moreover, the cannabinoid-induced effects were prevented when animals were pretreated with the μ-opioid receptor antagonist naloxone, neutralizing antibodies to β-endorphin, or when μ-opioid receptor-deficient mice were used (361). These findings clearly indicate a crucial role for epidermally derived β-endorphin in nociception. Thus cannabinoids and β-endorphin synergistically regulate peripheral acute, inflammatory, and neuropathic pain.

In contrast to pain, less is known about the impact of β-endorphin in cutaneous neurogenic inflammation. Recent findings point to an involvement of β-endorphin in the pathophysiology of acne (972) and atopic dermatitis (65, 67), although direct evidence is still lacking. Animal studies, however, indicate that β-endorphin also has a role in cutaneous inflammatory processes. For example, hindpaw inflammation generates a marked upregulation of opioid peptides in the skin, although the cell source was not analyzed (802).

12. Enkephalins

The endogenous opioid peptides [Met]-enkephalin and [Leu]-enkephalin are known to suppress a number of elements of the immune response, including antimicrobial resistance, antibody production, and delayed-type hypersensitivity (681). In the skin, application of [Met]-enkephalin induced a flare reaction, reducible by pretreatment with antihistamine, suggesting both histamine and histamine-independent involvement of enkephalins in neurogenic inflammation (586). [Met]-enkephalin induced infiltration of dermal lymphocytes, monocytes, and macrophages, and enkephalins protect against tissue damage caused by hypoxia and inhibit differentiation and proliferation of keratinocytes (226, 586). Increased amounts of enkephalins were reported in the lesional skin of psoriasis patients. Enhanced levels of enkephalins are reduced in parallel with the clinical improvement induced by a topical vitamin D analog and a corticosteroid. Thus because enkephalins can modulate epidermal differentiation and inflammatory processes, these findings indicate that enkephalins may play a role in the pathogenesis of psoriasis (585).

13. Dynorphin

Dynorphin, an opioid neuropeptide found in the central and peripheral nervous systems, is a neurotransmitter as well as an immunomodulatory molecule. The presence of Tyr-Gly-Gly-Phe-Leu (Leu-enkephalin) in the first five residues of dynorphin A, for example, categorizes the peptide as an endogenous ligand for opioid receptors. Kappa opioid peptide (KOP) receptor activation accounts for many of the biological activities of dynorphin. First identified for its role in nociception, dynorphin has since been shown to be involved in a range of central nervous functions, including mood, motor activity, homeostatic response to injury, and seizures. Further animal studies have shown that peptides derived from the gene encoding for preprodynorphin, dynorphin A, dynorphin B, and α-neoendorphin, are important neuromodulators (779).

Initial interest in the tridecapeptide dynorphin was fueled by the hope of developing anti-withdrawal agents for opiate-addicted patients. However, studies in humans failed to meet these demands, probably due to dynorphin's short duration of action (294).

In the skin, studies on dynorphin-mediated effects primarily focused on the role of nociception and modulation of hyperalgesia in the inflamed tissue. Immunohistochemical studies in animals revealed the presence of dynorphin A predominantly in sympathetic axons innervating the cutaneous venous bed, but also in sensory nerve fibers, Merkel cells, and immune cells within the inflamed tissue (557, 802). The discovery of inhibited nociception during inflammation by endogenous opioids increased interest in this neuromodulatory peptide. Leukotriene A_4 hydroxylase was shown to lose its aminopeptidase activity in the presence of the dynorphin fragment-(1—7) and may thereby support the maintenance of inflammation in psoriasis and atopic dermatitis (587).

Although therapeutic applications of dynorphin during inflammation, pain, and pruritus are still dreams of the future, effects of dynorphin on keratinocyte migration in wound healing might be a promising target (65). With respect to this fact, an important issue in the future will be to better characterize the role of dynorphin in cutaneous cells and certainly the distribution and regulation of its receptor, the κ-opioid receptor.

14. MSH

Except for its potential to stimulate melanin production and its effect on UV-mediated melanogenesis, evidence is accumulating that α-MSH-(1—13) and its COOH-terminal tripeptide α-MSH-(11—13) are important molecules within the neuroimmune network. Several studies demonstrate a direct immunoregulatory and anti-inflammatory role for these POMC-derived peptides in the skin in vivo and cutaneous cells in vitro. α-MSH antagonizes the effects of proinflammatory cytokines such as IL-1α,

IL-1β, IL-6, and TNF-α or endotoxins (81, 321), suggesting that the immunosuppressive capacity of α-MSH is also mediated through its effects on monocyte and macrophage function (Table 2). Accordingly, α-MSH downregulates the production of proinflammatory cytokines and accessory molecules on antigen-presenting cells, whereas production of suppressor factors such as IL-10 is upregulated by α-MSH (281). Thus α-MSH may inhibit contact sensitivity and lead to hapten-specific tolerance by inducing anti-inflammatory cytokines. The opposite is also true; POMC genes can be regulated by proinflammatory early cytokines such as IL-1 and IL-6, for example (806).

The highest concentrations of α-MSH can be detected in the epidermis (862). With the exception of hair follicle keratinocytes, POMC peptides are not detected in normal skin. Several stimuli such as α-MSH itself, tumor promoters (phorbol myristate acetate) or UVB light, for example, induce upregulation of POMC mRNA in normal keratinocytes or melanocytes, respectively, indicating that POMC peptides exert biologic effects in the skin and are potent modulators of immune and inflammatory responses (495). For example, IL-1 has been found to enhance α-MSH production in keratinocytes in vitro (719). Moreover, UV light induces upregulation of POMC mRNA and protein as well as MC-1R at the RNA level in keratinocytes. Moreover, differentiation and proliferation of keratinocytes are modulated by POMC peptides including α-MSH, and γ-MSH-treated keratinocytes are more sensitive to oxidative stress, suggesting a regulatory role of MSH in keratinocyte homeostasis, survival, and cell protection. α-MSH also downregulates expression of heat shock protein hsp 70, indicating that MSH has a role in cytoprotection and cell survival (606).

Recent studies found that α-MSH acts as a selective inducer of secretory functions in human mast cells (1, 2, 300). α-MSH induced a dose-dependent release of histamine from isolated mast cells from human skin and from punch biopsies of the skin. However, no effect of α-MSH was seen regarding the expression of IL-1, IL-6, IL-8, TGF-β, and TNF-α. In addition, MC-1R was identified at the transcriptional level by RT-PCR analysis, but not at the protein level, whereas, in leukemic human mast cells (HMC-1), the mRNAs and the proteins for the MC-1R and MC-5R were identified (29). These results suggest that α-MSH may selectively induce acute inflammatory effects via secretion of histamine, probably via MC-1R.

Treatment of cultured fibroblasts with α-MSH results in upregulation of matrix metalloproteinase-1 (MMP-1) (435), probably via stimulation of MC1-R, suggesting that α-MSH regulates the function of collagenases in the connective tissue. Moreover, α-MSH induced IL-8 mRNA expression and release in dermal fibroblasts (434). In fibroblasts, POMC production was stimulated by TNF-α and downregulated by TGF-β (859). TNF-α increased β-endorphin and ACTH levels, whereas TGF-β-stimulated fibroblasts showed increased ACTH but not β-endorphin and α-MSH release. Moreover, fibroblast-derived β-endorphin induced histamine release, demonstrating a possible role in extracellular matrix deposit regulation and skin inflammation (858).

Dermal endothelial cells have been shown to upregulate POMC mRNA after treatment with UV light or IL-1β (737). MC-1R expression was increased in these cells when stimulated with IL-1β or α-MSH itself. Moreover, human dermal microvascular endothelial cells express MC1-R, and α-MSH induces increased levels of IL-8 and modulates the production of chemokines such as IL-8 or Gro-α (82, 321).

Locally as well as systemically, α-MSH impaired immunologic functions in vivo (328, 770), downregulated the costimulatory molecule CD86 on monocytes and macrophages, and induced anti-inflammatory cytokines such as IL-10 in vitro (63). In monocytes, α-MSH was found to downregulate MHC class I expression and to inhibit the expression of CD86 (B7–2), whereas MHC class II and CD80 (B7–1) expression were not significantly changed (62). Recent studies further indicated that some of the anti-inflammatory properties of α-MSH on the cellular level appear to be mediated by the downregulation of NFκB (122, 327, 364, 409). Further details about the role of POMC peptides in inflammatory and immune disorders are described in section x.

15. Melanocortin receptors

POMC peptides exert their effects via five subtypes of heterodimeric G protein-coupled receptors with seven transmembrane domains designated as melanocortin receptors (MC-1R through MC-5R) (171). Several different signaling pathways have been described, depending on receptor subtype and tissue specificity, including intracellular Ca^{2+} mobilization and cAMP elevation. In melanoma cells, α-MSH elevated cAMP levels, leading to activation of p44/MAP-kinase and AP-1 which may activate tyrosinase synthesis (235). MC-Rs differ in their tissue distribution and affinity for POMC peptides (171). MC1-R is the predominant receptor in the skin and exhibits the highest affinity for α-MSH and ACTH, respectively (496, 945). Pharmacological stimulation of MC1-R can be achieved by the synthetic agonist "compound 2" (331). MC1-R is the only receptor so far identified that may explain variation in skin color, freckles, and sun sensitivity (401, 668). Endothelial cells, fibroblasts, keratinocytes, epithelial cells of eccrine, apocrine and sebaceous glands, as well as hair follicles, monocytes, melanocytes, and monocytes express MC1-R (786), whereas muscle cells and adipocytes express MC2-R and MC5-R (80). Others have shown that MC-5R is localized in sebaceous glands, eccrine glands, hair follicles, and epidermis of human and rat skin, cultured human sebocytes, and rat preputial cells

and have suggested a crucial role for melanocortins in sebum production (861, 957). Finally, UVB treatment leads to upregulation of MC1-R in cultured keratinocytes (153, 378) and dermal microvascular endothelial cells (737). MC1-R was recently found to mediate a female-specific mechanism of analgesia in humans (545).

Agouti is a gene locus found in rodents and humans that encodes a skin peptide that modifies coat color by antagonizing activation of MC1R in mice. The gene product, agouti signaling protein (ASIP), was identified as a high-affinity antagonist of different MCR subtypes and is involved in determining mouse coat color, for example (493, 835). The Agouti protein is normally expressed in the skin where it affects pigmentation and acts as an antagonist of the melanocyte receptor for α-MSH (MC1R). Recent observations in non-agouti-lethal 18H (a18H) mice further suggest a role of agouti gene products and MCRs in pruritus and other immunological diseases that involve the skin (635). These mice develop a spectrum of immunological and inflammatory diseases of the large intestine, pulmonary chronic interstitial inflammation and alveolar proteinosis, inflammation of the glandular stomach and skin resulting in scarring due to constant itching, and hyperplasia of lymphoid cells, hematopoietic cells, and the forestomach epithelium. Previous studies suggested that the a18H mutation results from a paracentric inversion that affects two loci: agouti and another, as yet unidentified locus designated the itch gene, which is responsible for the immunological phenotype of a18H mice. Mutation of a18H results from an inversion, and the itch gene encodes a novel E3 ubiquitin protein ligase, a protein involved in ubiquitin-mediated protein degradation. These results clearly indicate that ubiquitin-dependent proteolysis is an important mediator of immune responses in vivo and provide evidence for a role of the itch gene in inflammation and the regulation of epithelial and hematopoietic cell growth. However, the role of agouti gene products and mutations in pruritus and skin immunology awaits further study.

16. Cannabinoids and receptors

In the 19th century, marijuana was prescribed by physicians for the treatment of maladies and diseases, including eating disorders (appetite stimulant), arthritis, tooth pain (pain relief), rabies (muscle relaxant), and gonorrhea. However, as the potential addictive potential of marijuana was realized, its use as a therapeutic agent became restricted.

D9-tetrahydrocannabinol (THC) is the best known exogenous cannabinoid found in marijuana. Additionally, the body itself produces cannabinoids, defined as endocannabinoids. In humans, endocannabinoids are preferentially generated when stimulated by lymphocytes and macrophages (145, 437, 502).

The naturally occurring endocannabinoids are produced by the cleavage of membrane fatty acids, in particular arachidonic acid, and have varying specificities for the two cannabinoid receptors. Arachidonoylethanolamide (AEA; previously known as anandamide) is an endogenous fatty acid amide and was the first endocannabinoid to be discovered (208). It has higher affinity to CB1 than CB2 and also binds to the TRPV1 ion channel (974). Several other endocannabinoids have been described, including 2-arachidonoylglycerol (2-AG) and 2-arachidonylglyceryl ether (noladin ether), the former being a full agonist of CB2 and the latter showing a higher affinity for CB1 (828). The endocannabinoids are produced by various cells, including cells of the immune system and the PNS and CNS.

Synthetic cannabinoid analogs also exist (e.g., CP55,940, WIN55,212–2), high-affinity ligands for both CB1 and CB2. In contrast, JWH-015 prefers activation of CB2. The selectivity is of importance since the psychoactive effects of cannabinoids are mediated via CB1, not CB2. Finally, receptor antagonists such as SR141716A and SR144528 have been synthesized (352) that inhibit or reverse the biological effects of CB1 and CB2 agonists. These antagonists have been used experimentally to determine the receptor binding activities of various putative agonists and are now used clinically as CB1 antagonists.

The role of cannabinoids in the regulation of peripheral neuronal effects is only partly understood (Table 2). Peripherally administered cannabinoids provoke antinociceptive and antihyperalgesic effects both in rats (352) and humans (reviewed in Refs. 175, 502, 674). In addition to neurons, CB have been also identified on immune cells (208, 827). In general, CBs mostly inhibit the production of cytokines during innate and adaptive immune responses, both in animal models and in humans in vitro and in vivo (54, 438, 439). Their suppression of proinflammatory cytokine and chemokine production indicates that these drugs might have anti-inflammatory effects and could therefore be used to treat chronic inflammatory diseases. For example, macrophages express CB2 (974). During infection, bacterial-derived LPS stimulates the release of anandamide from macrophages, mononuclear cells (PBMCs), and dendritic cells. Accordingly, immune cells both in humans and rodents increase the production of endocannabinoids in response to LPS in vivo. Functional studies further indicate a role of macrophage-derived CB2 in the progression of autoimmune diseases such as multiple sclerosis (524, 564) or HIV (440). In addition, 2-AG attracts human eosinophils (598), as well as B cells (666) and dendritic cells (503) in vitro, and THC produces decreased levels of interferon (IFN)-γ after stimulation with LPS. Moreover, serum levels of TNF-α and IL-12 were shown to be decreased in mice that were primed by infection with *Propionibacterium acnes* and stimulated with an injection of LPS before treatment with

cannabinoids (THC and analogs) (777). Thus cannabinoids protected these mice from the lethal effects of LPS that have been mediated, at least in part, by cytokine regulation such as IL-10, for example. Accordingly, cannabinoids also downregulate the release of IL-1, TNF-α, and the chemokine CXCL8 during injury in mice, suggesting that cannabinoids are anti-inflammatory because they suppress cytokine, chemokine, and TNF-α effects. Under certain conditions, however, cannabinoids are also capable of increasing the production of cytokines (TNF-α, IL-1, IL-6, and IL-10) when coadministered with bacteria or antigens (778, 966), or also alone (204, 433). In mice, agonists of the CB2 reduce cutaneous edema, probably by an indirect effect on mast cells via a thus far unknown mediator (395).

Thus, in vivo and in vitro, cannabinoids may either suppress or enhance the production of inflammatory mediators, depending on the nature of the proinflammatory stimulus, the application form, or the type of cannabinoid used. Further research is needed to clarify these observations.

17. Cannabinoids are involved in T-cell regulation

THC induces suppression of both TH1-cell activity and cell-mediated immunity in mice infected with *Legionella pneumophila* (577) and decreases the production of IFN-γ and IL-12, as well as the expression of IL-12 receptor (IL-12R), but increases the production of IL-4 (965). These data suggest that cannabinoids suppress TH1-cell activity and increase TH2-cell activity, or activate regulatory T cells, either T regulatory 1 (TR1) cells or TH3 cells (639). Thus cannabinoid receptors expressed by T and B cells or by antigen-presenting cells may suppress immune responses and inflammation towards a TH2-cell-dominated profile.

CB1 and CB2 are seven-transmembrane, G protein-coupled receptors that are coupled to G(i/o) heterotrimeric proteins, and thereby inhibit adenylyl cyclase activity and downstream second messengers such as Ca^{2+} and MAPKs, for example (202). In mast cells, cannabinoids also induce cAMP signaling, thereby mediating anti-inflammatory responses (772). They also activate inward-rectifying K^+ channels on neurons. However, recent findings suggest that CB receptors are coupled to several G proteins, depending on the system studied. Moreover, cannabinoids can also couple to non-CB receptors such as TRPV ion channels, for example (890).

The expression of endocannabinoid receptors can be modulated by LPS or other inflammatory agents on immune cells such as T lymphocytes, for example (Jurkat T cells) (87, 437). However, little is known about the molecular regulation of the genes encoding for CB receptors in immune and inflammatory cells. In vivo, application of the endogenous cannabinoid receptor agonist anandamide elicited hypothermia, catalepsy, impaired motor activity, and antinociception (617, 891).

In the skin, expression of CB1 and CB2 was detected in neurons, keratinocytes, cutaneous mast cells, and macrophages by immunofluorescence (790). Recently, a role for the endogenous cannabinoid AEA could be demonstrated in an immortalized human keratinocyte cell line (HaCaT) and normal human epidermal keratinocytes (NHEK). Both cells express CB1R, a selective AEA membrane transporter (AMT), an AEA-degrading fatty acid amide hydrolase (FAAH), and an AEA-synthesizing phospholipase D (PLD). Interestingly, the activity of AMT and FAAH increased while the endogenous levels of AEA decreased in HaCaT and NHEK cells when the cells were stimulated by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and calcium. In vitro, AEA inhibited the formation of cornified envelopes through a CB1R-dependent reduction of transglutaminase and protein kinase C activity, and inhibited AP-1, suggesting an important role of cannabinoids in epidermal differentiation and skin development (501).

CB2Rs may be involved in the regulation of pain and pruritus in cutaneous sensory nerves. In a recent study, CB2R inhibited acute, inflammatory, and neuropathic pain responses in the skin. In a mouse model, CB2R activation induced the release of β-endorphin from keratinocytes, which in turn stimulated μ-opioid receptors on primary afferent neurons, thereby inhibiting nociception in vitro and in vivo. These functional data were supported by the immunohistological finding of CB2R colocalization in β-endorphin-containing keratinocytes in the stratum granulosum. Thus keratinocytes may play an important role in the communication network between the skin and sensory nerves (361).

CB1 and TRPV1 show a marked colocalization in sensory neurons, and the endogenous cannabinoid anandamide also stimulates TRPV1, thus doubling its endovanilloid properties, depending on its concentration and other local factors (203a, 214). Indeed, CB1 agonists effectively suppress histamine-induced pruritus (225), suggesting the involvement of CB1 signaling in the initiation of itch and pain. At higher concentrations or under inflammatory conditions, cannabinoids also activate the TRPV1 pathway and thereby switch their neuronal effect from inhibition to excitation and sensitization.

Cannabinoid receptors, similar to TRPV1, are also expressed by nonneuronal human skin cells like mast cells and keratinocytes (501, 790). Thus cannabinoid receptors may be involved in the neuronal-nonneuronal cellular network of pruritogenic stimuli arising into and from the skin. That speculation could lead one to hypothesize that coadministration of a TRPV1 agonists with a CB1 agonist may serve as a potent antipruritic and antinociceptive regimen. For example, a combination might prevent the acute burning sensations induced by capsa-

icin, because CB agonists (e.g., AEA, HU210) would prevent the excitation induced by capsaicin (676, 692).

Recent studies in animal models and in humans have generated promising results for the use of cannabinoid compounds to treat various disorders such as edema, vascular inflammation, pain, pruritus, arthritis, cancer, neurological disorders, and obesity, on the basis of the immunomodulatory and anti-inflammatory capacities of cannabinoids.

18. CRH

The role of corticotropins in skin physiology and pathobiology has been intensively reviewed (769, 770). CRH is a 41-amino acid residue peptide, originally secreted by the pituitary upon stimulation from the hypothalamus-derived corticotropin-releasing factor (CRF) is a potent mediator of the neuroimmunoendocrine axis. CRF is capable of producing CRH and the related urocortin peptide. CRH expression is highly responsive to common stressors such as UV radiation or immune cytokines (174, 766) (Table 2). Likewise, in the HPA axis, CRH is recognized as a central regulatory element of chronic stress. In addition, CRH acts as a proinflammatory mediator and induces skin mast cell degranulation, thereby increasing vascular permeability. In contrast, administration of CRH has anti-inflammatory effects in thermally injured skin, and together with urocortin reportedly inhibited proliferation of keratinocytes and induced keratinocyte differentiation (955). The actions of CRH and urocortin in the skin have been extensively reviewed recently (769, 771).

19. CRH receptors

The gene coding for human CRH-R1 contains 14 exons. Seven alternatively spliced CRH-R1 transcripts are known (CRH-R1α, CRH-R1β, CRH-R1c, CRH-R1d, CRH-R1e, CRH-R1f, CRH-R1g, and CRH-R1h). The CRH-R2 exist in three major forms (CRH-R2α, β, and γ) (reviewed in Ref. 771). Recent studies demonstrated that the human skin expresses high levels of CRH receptors that belong to the GPCR family that has seven transmembrane domains. In human skin, the CRH receptor CRH-R1α was expressed in all major cellular populations of epidermis, dermis, and subcutis. The CRH-R2 immunoreactivity was localized predominantly in hair follicles, sebaceous and eccrine glands, muscle, and blood vessels (767).

20. Secretoneurin

Secretoneurin is a recently discovered 33-amino acid neuropeptide derived from secretogranin II (chromogranin C), which is found in sensory afferent C fibers of different tissues including the skin and is coreleased from afferent nerve endings together with SP and CGRP (404, 935). Secretoneurin triggers the selective migration of monocytes (403), modulates chemotactic activity of neutrophils (742) and eosinophils (224), and inhibits proliferation but stimulates migration of endothelial cells in vitro (405). Moreover, secretoneurin induces migration of human skin fibroblasts but does not stimulate their proliferation. This effect appears to be mediated by the COOH-terminal fragment of this neuropeptide (402). Taken together, these finding indicate that secretoneurin modulates inflammatory responses in the periphery, including the skin. However, the role of secretoneurin in cutaneous inflammation remains unknown.

21. Other neurohormones and their receptors in the skin

Several neuropeptides and neurohormones and their receptors are generated from sensory nerves or cutaneous cells under physiological or pathophysiological conditions (Table 2). Others include parathyroid hormone releasing factor (PTHrP), GH, prolactin, galanin, dynorphin, neurotensin, gastrin-releasing peptide (GRP), NPY, glutamate, aspartate, endorphins, enkephalins, cannabinoids, bradykinin, serotonin, cholecystokinin, thyroid hormones, endothelins, adenine or adenosine nucleotides (ATP) and their purinergic receptors, adrenomedullin, and L-DOPA. For most of them, specific high-affinity receptors have been detected in the skin and/or in immunocompetent cells, indicating a role of these peptides in skin homeostasis and within the neuroimmunological network (reviewed in Refs. 769, 805, 811, 816).

IV. ACETYLCHOLINE, CATECHOLAMINES, AND THEIR RECEPTORS

Acetylcholine, epinephrine, and norepinephrine are small nonpeptide messengers that are produced both by neurons and nonneuronal cells of various tissues including the skin (reviewed in Ref. 769). Originally, these molecules were described as important mediators released from autonomic nerve fibers. Recent studies suggest that adrenergic and cholinergic transmitters play important roles in cutaneous homeostasis and inflammation (285, 713) (Table 2).

A. ACh and Receptors

ACh is synthesized in cholinergic neurons from choline, which is synthesized locally from pyruvate by acetyl coenzyme A, and taken up by nerve endings. Choline acetyltransferase (CAT) acetylates choline to form ACh in the cytosol, which is then inserted into secretory granules in the nerve ending. Depolarization of the nerve ending allows calcium influx by a voltage-dependent Na^+ chan-

nel, to induce the release of ACh into the extracellular space. Released ACh interacts with muscarinic and nicotinic receptors on the plasma membrane of target cells. Once released, ACh is efficiently degraded by acetylcholinesterase (AChT). The choline that is generated by acetylcholinesterase is transported back into the nerve ending by high-affinity transporters, where it can be reused for ACh synthesis.

ACh has been detected in autonomic nerve fibers (725), melanocytes (369, 466), and keratinocytes of human skin (289) as well as in lymphocytes (57, 677). It regulates different activities in keratinocytes, such as proliferation, adhesion, migration, and differentiation. ACh was shown to be crucial to sustain the viability of keratinocytes in vitro, and cholinergic drugs were capable of modulating keratinocyte function such as adhesion and motility. Intracellular calcium appears to be an important signaling molecule to mediate these effects on keratinocytes after stimulating specific ACh receptors (285). Both choline acetyltransferase (ACT) and acetylcholinesterase (AChE) appear to regulate the function of ACh in keratinocytes. While choline acetyltransferase was detected in all epidermal layers of human skin, acetylcholinesterase is more confined to basal keratinocytes (287, 575). Intracutaneous application of ACh has been demonstrated to modulate various inflammatory responses (see sect. IX). For example, iontophoretically administered ACh on the skin produced vasodilatation (371). Moreover, increased AChE levels combined with decreased ACh levels were observed in acute burn lesions and dystrophic epidermolysis bullosa (42, 218, 516).

1. ACh receptors

ACh and its derivatives exert their effects by activating nicotinergic or muscarinergic cell surface receptors (629, 630). The nicotinic receptors for ACh are transmembrane ion channels formed of α1, α2, β, γ, and ϵ. Interaction of ACh with binding sites of the α-subunits permits the efflux of K^+ and the influx of Na^+, causing depolarization of cells. In contrast, muscarinic receptors belong to a subfamily of GPCRs with seven transmembrane domains, defined as m_1, m_2, m_3, m_4, and m_5 receptors. These receptors have all been cloned and well characterized (152, 285, 357). Muscarinergic receptors have been detected in melanoma cell lines in vitro (446, 588), keratinocytes (285, 287, 288, 290), fibroblasts (123), and endothelial cells (308). In rat skin, the m_2 receptor was detected in nerve fibers (308) where it may be involved in pain and nociception (798).

Human keratinocytes generate ACh, CAT, AChE, and both muscarinergic as well as nicotinergic receptors (285). Nicotinergic receptors show a marked variability of either α3-, α5-, α6-, α7-, β1-, β2-, or β4-subunits, respectively (287, 288, 290). Although α5 was detected homogeneously throughout all epidermal layers, the α3-, β2-, and β4-subunits seem to be restricted to the upper epithelium (288). Expression of these subtypes appears to be stage dependent during keratinocyte differentiation (285, 287, 575). In vitro, nAChRs influence motility, differentiation, and cell survival of keratinocytes (287, 289, 290). However, the muscarinergic receptor system may be required for proliferation (285). In a similar fashion, nicotinergic and muscarinergic pathways stimulate keratinocyte cell adhesion (285) and influence keratinocyte migration via α3 and α7 nicotinergic receptors (967). Finally, a cloned cholinergic receptor contains an α9-subunit and shows both muscarinergic as well as nicotinergic characteristics (578).

Keratinocytes also generate various muscarinic receptor subtypes such as the m_1, m_3, m_4, and m_5 (285). Recently, m_2 receptor distribution was described in rat skin (308). Again, the expression of the receptor subtype is strictly regulated during keratinocyte maturation. However, the fine-tuned interaction of the several muscarinergic receptor subtypes with the ligand is still incomplete (578). For example, endogenous ACh may generate various biologic effects in human keratinocytes at different stages of cell differentiation by activating specific subtypes of cholinergic receptors.

AChRs reportedly may be involved in the formation of blisters in pemphigus vulgaris. Pharmacological blockade of AChRs with either muscarinic or nicotinic antagonists, atropine, and mecamylamine results in pemphigus-like acantholysis of human keratinocytes (285, 579, 911), widening of the intercellular space, and loss of desmosomes (286, 579). In an experimental model of pemphigus vulgaris (PV), PV antibodies acted as antagonists at the AChR on keratinocytes and induced acantholysis by inhibiting AChR stimulation, thereby altering the normal control of keratinocyte adhesion and motility (578).

2. Macrophages and the cholinergic anti-inflammatory pathway

An important mechanism that links peripheral local inflammation with central nervous control has been recently described, defined as the so-called anti-inflammatory cholinergic pathway (88, 875). According to this new understanding of neuroimmunomodulation, the parasympathetic part of the autonomous nervous system has been found to play an important role in the control of immunity and inflammation (Fig. 4, Table 2). During inflammation, afferent vagal neurons transmit immune signals to the brain, and vice versa, and activation of the vagal efferent fibers leads to suppression of inflammation. This interaction of sensory afferent and motor efferent vagal neurons is a centrally integrated reflex mechanism that controls inflammation in real time. Therefore, the α7-subunit of the ACh receptor could be identified as a molecular mediator

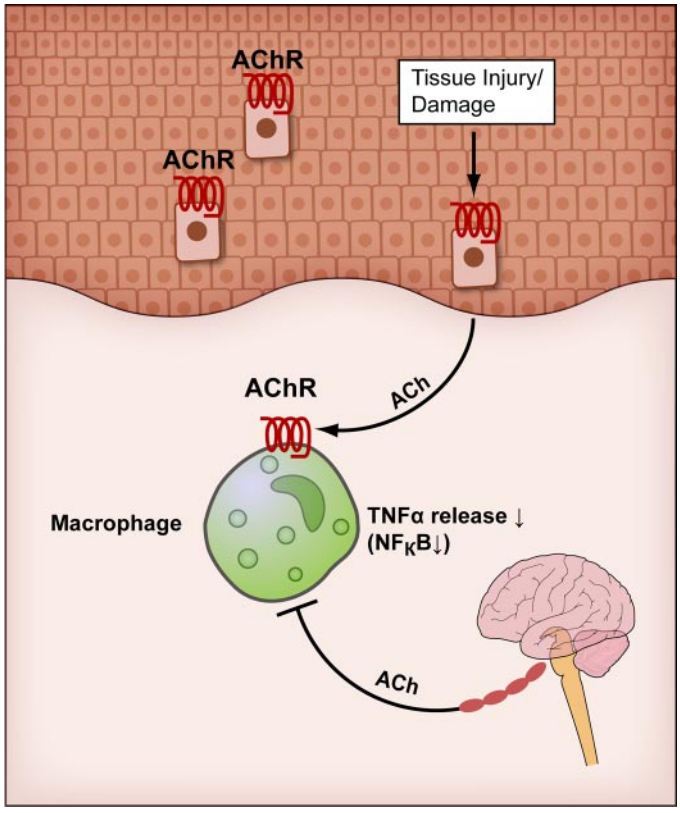

FIG. 4. Anti-inflammatory role of acetylcholine in macrophage regulation and skin function. During inflammation, tissue injury, or immune challenge, activated macrophages and other immune cells that express ACh receptors may be activated by ACh (see text for details). In the skin, ACh can be released by the efferent autonomic nervous system and by keratinocytes, for example. This stimulation leads to downregulation of TNF-α release and NFκB activation thereby modulating immune responses in the skin.

of inflammation control in the anti-inflammatory cholinergic pathway (920). Stimulation of α7 nAChR leads to reduced transcription of NFκB and thus inhibits the release of TNF-α, IL-1β, and HMGB-1, important mediators of systemic inflammation (533). Indeed, this neuroimmunomodulatory effect of the afferent vagus has been demonstrated in the heart, liver, spleen, gut, and recently in the skin. In the skin the cholinergic anti-inflammatory pathway accounts for endothelial activation and leukocyte recruitment through the dermal microvasculature (698).

Together, these findings clearly demonstrate a substantial role of the cholinergic anti-inflammatory pathway for the fine-tuned regulation of inflammation (Fig. 3).

B. Catecholamines and Receptors

1. Catecholamines

Catecholamines are expressed by the CNS and PNS, especially in postganglionic sympathetic nerves that principally innervate ganglia, blood vessels, and smooth muscle cells. Moreover, human skin has the full capacity to generate catecholamines, their degrading enzymes, and high-affinity receptors. Norepinephrine (NE) is synthesized from tyrosine in adrenergic nerve terminals. Tyrosine, which is taken up by nerve endings, is converted to dopa by tyrosine hydroxylase, the rate-limiting enzyme for both norepinephrine and dopamine synthesis. Dopa decarboxylase converts dopa to dopamine, which is packaged in secretory vesicles. Within secretory vesicles, dopamine β-hydroxylase converts dopamine to NE. Once released by exocytosis, NE interacts with adrenergic receptors on target cells to regulate their function. The actions of NE are mainly terminated by rapid reuptake into nerve endings by a cocaine-sensitive transport mechanism. A transporter in neuronal membranes binds sodium, chloride, and NE or related amines and transports them to the cytoplasmic face of the membrane, where NE is released. NE is then transported into vesicles or is deaminated by monoamine oxidase (MAO) in the mitochondria. Some NE is also taken up by target cells, where it may be inactivated by MAO.

In the skin, catecholamines and their regulating enzymes have been detected in nerve fibers (420), keratinocytes (715, 718), and melanocytes (714, 715, 717). Moreover, catecholamines may regulate the activity of certain lymphocytes (natural killer cells) (610) and monocytes (687, 946) and induce apoptosis in lymphocytes (166). Catecholamine release may be also induced by lymphocytes such as T cells and B cells (445). During delayed type hypersensitivity (DTH), NE may also serve as an immunoenhancing agent (210). The same study that reached that conclusion also demonstrated that low-dose epinephrine significantly enhanced the DTH reaction in rat skin and dramatically increased the number of T cells in lymph nodes draining the site of the DTH reaction, supporting a role for this agent during cutaneous inflammation. Moreover, short-term exposure of bone marrow-derived DC to norepinephrine hampers IL-12 production and increases IL-10 release. The NE effect was mediated both by β- and α2-adrenergic receptors. The capacity of NE-exposed DC to produce IL-12 when cross-linked with CD40 and to stimulate allogeneic T-helper (Th) lymphocytes was reduced. These results suggest that the extent of Th differentiation in the response to an antigen might be influenced by the local sympathetic nervous activity in the early phase of dendritic cell stimulation (504).

Keratinocytes exert full capacity for biosynthesis and degradation of catecholamines (713). They produce epinephrine, norepinephrine, the cofactor (6R)L-erythro-5,6,7,8-tetrahydrobiopterin (6-BH4) as well as β2-adrenoreceptors (β2AR). The highest expression of these molecules can be detected at early stages of differentiation correlating with increase of intracellular [Ca^{2+}] concentrations in keratinocytes in response to catecholamines

(714). These results suggest an important role of this signaling system in epidermal homeostasis.

Melanocytes are also capable of producing the whole repertoire of the catecholamine system including transmitters, enzymes, and receptors. 6-BH4, for example, regulates melanogenesis (717). In patients with vitiligo, upregulation of 6-BH4 and monoamine oxidase was observed in keratinocytes, which may lead to increased norepinephrine levels and β2AR density (716). Moreover, increased 6-BH4 levels are cytotoxic for melanocytes (712, 714).

C. Adrenergic Receptors

Adrenergic receptors belong to a subfamily of GPCRs and comprise some of the most intensively studied members of this family of receptor molecules. Although originally identified as α- or β-receptors, many subtypes are known to exist, including α_{1a}-, α_{1b}-, α_{2A}-, α_{2B}-, α_{2C}-, and α_{2D}-, as well as β_1-, β_2-, and β_3-adrenergic receptors (ARs). α- and β-ARs were detected in keratinocytes and melanocytes of human skin (219, 220, 715, 813, 814). Additionally, β-AR agonists inhibited TNF-α release from mast cells (72) and are potent inhibitors of the IgE-mediated release of tryptase mediators from human mast cells in vitro (834). α- and β-ARs may also regulate important vascular responses in the skin such as vasoconstriction (215, 319).

Variations in adrenergic receptor density or function may be responsible for the pathophysiology of different skin diseases. For example, decreased levels of β-ARs were observed in lesional and nonlesional skin of psoriasis patients (815), whereas increased levels of α-AR were observed in arterioles of patients with scleroderma (250). Moreover, the β-AR appears to promote hair cycle progression (97, 637). Finally, epinephrine as well as norepinephrine were able to increase LPS-induced IL-6 production in human microvascular endothelial cells via β_1- and β-ARs (279).

V. NEUROTROPHINS AND NEUROTROPHIN RECEPTORS

A. Neurotrophins in the Skin

The mammalian skin expresses a variety of neurotrophic growth factors such as nerve growth factor (NGF), brain-derived nerve growth factor (BDNF), neurotrophin-3, and neurotrophin-4/5 (NT-3, NT4/5), which are essential for growth, proliferation, and maintenance of nerves. Cutaneous neurotrophins are expressed by sensory and sympathetic neurons and nonneuronal cells (325, 910), thereby regulating various biological modalities such as nocioception, proprioception, mechanoreception, nerve growth and development, apoptosis, epidermal homeostasis, inflammation, hair growth (93, 94, 96, 98, 620), and melanogenesis (56, 262, 278, 324, 431, 615) (Table 2). Several observations suggest that neurotrophins participate in the neuroimmunological network. For example, cutaneous application of neuropeptides such as cholecystokinin-8 enhances NGF expression in the skin (508). Moreover, the expression of NGF as well as NT-3, -4, and -5 can be induced by cytokines such as IL-6 and sIL-6R (517). Recently, enhanced expression of NGF mRNA was described in mast cells and keratinocytes, less in fibroblasts of patients with atopic dermatitis (297).

B. NGF and NT Receptors

Various receptors for nerve growth factor and neurotrophins are expressed in the skin and constitute the tyrosine (trk) and p75 pan-neurotrophin (p75NTR) family. Trk receptors show more restricted ligand specificity, whereas all neurotrophins are able to bind to p75NTR. TrkA and TrkB are high-affinity receptors for NGF and NT-3, respectively, while NT-3 also binds TrkC with low affinity (480, 625, 644, 685, 734, 950). In addition, p75NTR, NT-4/5 is also capable of binding TrkA and TrkB (688). One important function of p75NTR is the enhancement of NGF signaling via TrkA by increasing TrkA tyrosine autophosphorylation, suggesting an interaction among these receptor subtypes for neurotrophin-induced signaling (901).

NGF and NT receptors can be detected on sensory nerves (480, 678), keratinocytes (213, 644, 878), melanocytes (262, 950), fibroblasts (324), mast cells (947), hair follicles (92–94, 98), and various immune cells (45, 468a, 543, 753), indicating an important role for these molecules in cutaneous homeostasis. An adequate innervation seems to be necessary for the expression of p75NTR in keratinocytes, suggesting a role for nerve-derived NGF in the maintenance of epidermal integrity and wound healing (489).

NTs and their corresponding receptors modulate various functions of cutaneous nerves such as growth, development (480, 678), and apoptosis (604, 605). Recent findings suggest that neurotrophin expression also changes during aging. Thus degenerative and regenerative events during aging appear to be associated with changes in neurotrophic interactions between sensory neurons and target cells (56). During embryogenesis, NGF stimulates growth and neurite development in sensory cells (478) and is essential for reinnervation of the skin after injury to cutaneous nerves (209, 850). NGF is crucial for survival of nociceptive neurons during development and for nociception and neurogenic inflammation in adults. For example, NGF is upregulated and released by mast

cells and specifically binds to high- or low-affinity receptors on neuronal and nonneuronal cells, thereby contributing to cutaneous inflammation or injury. Moreover, overexpression of NGF in mouse skin increased the number of sensory neurons and expression of TrkA and TrkC (276), indicating a regulatory role for NGF in the cutaneous nervous system.

NT-3 is essential for the development of cutaneous sensory nerves. BDNF or NT-4/5 activate sensory neurons and elicit hyperalgesia. NT-3 supports the postnatal survival of primary sensory neurons that mediate mechanoreception and their Merkel cell containing touch dome end organs (7, 8). Cutaneous sensory innervation is selectively restored by NT-3, since overexpression of NT-3 in the skin of NT-3(−/−) knockout mice rescued most cutaneous neurons lost in NT-3(−/−) mice, but was unable to rescue NT-3-dependent neurons that project to noncutaneous sensory targets (456). These and other results suggest that NT-3 promotes the survival of a limited subpopulation of cutaneous sensory neurons (593). Additionally, NT-3 inhibits experimentally induced inflammatory hyperalgesia in rats (925).

NT-3 and BDNF are required for the postnatal survival or functional maturation of sensory neurons. Moreover, an unexpected and marked acute loss of tactile sense in the rat hindpaw after adjuvant-induced inflammation can be observed (924). This effect was correlated with decreased expression of BDNF and, to a lesser extent, of NT-3 in the inflamed skin. Administration of BDNF but not NT-3 after inflammation accelerated the recovery of tactile sense. These results support a role of BDNF in the regulation of tactile sense and neurogenic inflammation. Finally, BDNF or NT-4/5 activates sensory neurons and elicits hyperalgesia.

The neurotrophin survival dependence of peripheral neurons in vitro is regulated by proapoptotic factors such as BCL-2 and BAX. Moreover, the NGF/TrkA signaling system regulates cutaneous sensory innervation and is required for the full phenotypic differentiation of sensory neurons (618).

In keratinocytes of various species, NGF regulates proliferation and differentiation (213, 644, 878). NGF also protects human keratinocytes from apoptosis via activation of the high-affinity NGF (trkA) receptor (644). Melanocyte survival and dendrite formation was enhanced by NGF after UV irradiation (262, 950). Recent results strongly indicate that keratinocyte NGF can be modulated by neuropeptides from sensory nerves in the skin (129). Prostaglandin E_2 and neuropeptides such as SP and NKA are capable of directly inducing NGF expression and secretion in human keratinocytes and upregulate NGF expression in murine epithelial cells after topical application of capsaicin. Keratinocyte NGF may be also increased after UV radiation and phorbol esters, suggesting a role for this neurotrophin in epidermal regeneration (213, 720, 878). Moreover, NGF produced by keratinocytes or endothelial cells may be critical for the reinnervation of wounded skin (213). During inflammation, NGF is markedly increased in nerves associated with the inflamed area (216, 932).

In addition to NGF, the neurotrophins BDNF, NT-3, and NT-4 are also expressed in the epidermis. In murine skin, muscle cells showed strong NT-3 immunoreactivity, whereas BDNF-IR was found only in skin nerve bundles. NT-4 immunoreactivity was noted in single epidermal murine keratinocytes. In human keratinocytes, PGE_2 enhanced the production of NT-4 via EP3 receptor activation in vitro. The in vivo relevance of this observation, however, has to be determined in humans (412). The high-affinity receptor for both BDNF and NT-4, TrkB, was detected in basal and suprabasal epidermal keratinocytes, whereas the high-affinity NT-3 receptor, TrkC, was observed in skin nerve bundles. Transgenic mice overexpressing BDNF or NT-3-overexpressing transgenic mice showed a significantly increased epidermal thickness and enhanced number of proliferating epidermal keratinocytes. Moreover, the number of keratinocytes was significantly reduced in BDNF knockout mice, and coadministration of NGF neutralizing antibody failed to abrogate the stimulatory effect of NT-3 on keratinocyte proliferation in vitro. Thus neurotrophins may be important modulators of keratinocyte physiology and epidermal homeostasis.

Hair cycle morphology and development may be regulated by NGF as well as neurotrophins (4, 93, 94, 96, 98, 620, 638). In mice, the p75 neurotrophin receptor has been shown to control apoptosis-driven hair follicle regression. Interestingly, significant catagen retardation was observed in p75NTR knockout mice compared with wild-type controls, indicating that neurotrophin receptors are involved in the control of keratinocyte apoptosis during catagen (92). Finally, human scalp skin and hair follicles were found to express NT-3 as well as its high-affinity receptor tyrosine kinase C (TrkC) and show hair cycle-dependent alterations in expression (4).

Melanocytes also express p75 NTF and trkA (625, 950). NGF is a chemoattractant for melanocytes that develop a dendritic shape in its presence (950). Moreover, UV-induced apoptosis in melanocytes appears to be decreased in the presence of NGF (956), probably by upregulating BCl-2 (956).

C. NGF and Cutaneous Inflammation

During inflammation, NGF is markedly upregulated in nerves associated with the inflamed area during inflammation (216, 659, 932), and NGF levels are increased in inflammatory skin diseases such as psoriasis (242). NGF also directly stimulates degranulation of mast cells, increases the number of mast cells in peripheral tissues and

promotes cell growth of myeloid cells (120, 411, 626), induces proliferation and differentiation of B cells, and enhances histamine release from basophils. NGF is also capable of stimulating IL-1 expression in PC12 cells and suppressing LTC_4 production in human eosinophils (13, 846). Of note, NGF is upregulated in patients with atopic dermatitis, in which it may contribute to pruritus, mast cell stimulation, eosinophil activation, and keratinocyte dysfunction (reviewed in Refs. 298, 622). This may account for a role of NGF in atopic dermatitis, a disease in which these cells are activated.

VI. ROLE OF CAPSAICIN AND TRANSIENT RECEPTOR POTENTIAL ION CHANNELS IN THE SKIN

Detailed information about TRP ion channels and their role in the skin can be found in other excellent reviews (70, 146, 147, 337, 453, 662, 805, 908) (Table 2).

Sensory neurons percept and transmit a wide range of stimuli such as temperature (from noxious heat to noxious cold). The observation that natural products that elicit psychophysical sensations of heat or cold, such as capsaicin or menthol, led to the hypothesis of the existence of "temperature receptors." In 1997, the first "heat receptor" (VR1 = TRPV1) was successfully cloned by Caterina et al. (151). This tremendous finding deepened our understanding of the pharmacological, biophysical, and biochemical results observed with capsaicin during the last decades more on the molecular level (see sect. III*A*). The vanilloid receptors belong to a subfamily of ion channels defined as transient receptor potential (TRP) cation channels. In addition to mild (>43°C) heat and acidosis, a panel of neuroimmune mediators of different origin (eicosanoids, histamine, bradykinin, ATP, various neurotrophins) is capable of either directly and/or indirectly activating TRPV1 (148, 151, 162, 360, 546, 757).

TRP channels make up six subfamilies: the canonical (TRPC), the vanilloid (TRPV), the melastatin (TRPM), the polycystin (TRPP), the mucolipin (TRPML) subfamilies, and the TRPA. In general, these molecules act as nonselective calcium-permeable sensory transduction channels sensing temperature and osmotic as well as mechanical changes (reviewed in Ref. 167).

TRP ion channels contribute to cutaneous thermosensation, osmoregulation, inflammation, and cell growth. Under pathological conditions such as inflammation or tissue injury, TRP are ultimately involved in signaling painful and pruritic stimuli to the CNS. Thus the identification of ion channels that detect heat or cold is now providing insight into the molecular basis of neurogenic inflammation, pain, and pruritus. Additionally, certain TRPs (TRPV1, TRPV4) seem to be directly involved in peripheral neurogenic inflammation.

A. TRPV1

Capsaicin has been intensively used to investigate the biology of sensory neurons and neurogenic inflammation. Topically applied capsaicin elicits a rapid sensation of burning pain by selectively activating small-diameter C fibers and triggers a cascade of inflammatory events such as erythema and release of proinflammatory mediators in skin and mucosa (Table 2). Although initial application of capsaicin activates sensory nerves to release neuropeptides, repeated applications render nerves in the treated area insensitive to further stimulation at higher concentrations, a phenomenon known as desensitization. This is probably caused by TRPV1-mediated depletion of neuronal-derived neuropeptides within a certain subdivision of sensory nerves (70, 343, 344). As a result, the nerve terminals become insensitive to capsaicin, as well as to other noxious stimuli. This observation led to the use of capsaicin as a potential agent for the treatment of various painful or pruritic diseases (175, 792).

Caterina et al. (151) successfully cloned the rat capsaicin receptor (VR1 = TRPV1) in an elegant study in which they used an expression cloning strategy based on calcium influx to isolate a functional cDNA encoding a capsaicin receptor from sensory neurons that encodes a protein of 838 amino acids with a predicted molecular mass of 95 kDa. It contains six transmembrane domains with an additional short hydrophobic stretch that represents a possible pore loop. This receptor was found to be a nonselective cation channel (with a small preference for calcium) that is structurally related to other members of store-operated calcium channels. However, protons do not mediate direct TRPV1 activation; rather, they sensitize by decreasing the receptor threshold so that ambient temperature stimuli become nociceptive "noxious" stimuli causing pain or allodynia (148).

TRPV1 is also a heat-gated ion channel that has been proposed to mediate responses of small-diameter sensory neurons to moderate (43°C) thermal stimuli. Moreover, TRPV1 is activated by protons, indicating that it may participate in the detection of noxious thermal and chemical stimuli in vivo. Low pH levels, which accompany local inflammation processes or ischemia, can also increase the response of the capsaicin receptor to noxious stimuli, suggesting that the response of sensory nerve fibers during "neurogenic inflammation" results, at least in part, from activation of capsaicin receptors through an excess of protons. Calcium or proton entry appears to regulate the activity of these channels probably by altering the level of phosphorylation (60, 61, 151, 837). Only recently, endogenous cannabinoids, e.g., anandamide, were shown to be full agonists at the TRPV1 (773, 974). In addition to protons, injury or inflammation produces a large variety of lipid-derived second messengers, such as anandamide or 12-HPETE which share structural similarity with cap-

saicin and may contribute to hyperalgesia by directly activating TRPV1 (360, 974). Recent structure-function studies suggest that capsaicin and these putative endogenous ligands (endovanilloids) bind to TRPV1 at the cytosol-membrane interface by interacting with residues located in a region spanning hydrophobic domains two through four (396). In accordance with that, Welch et al. (931) found that TRPV1 undergoes conformational changes upon capsaicin binding that it does not undergo in response to activation by protons or thermal stimuli. These structural rearrangements include the putative pore domain and reveal the location of an intracellular domain that contributes to the positive cooperativity seen for capsaicin activation.

Exogenous (capsaicin and ethanol) and endogenous (pH 6.0, noxious heat of 43°C, and anandamide) factors directly activate TRPV1 (151, 877, 890, 974). In addition, inflammatory agents that activate GPCRs (e.g., bradykinin and PGE_2) (355, 546, 664, 868, 895) and receptor tyrosine kinases (e.g., NGF) (162, 760) can indirectly sensitize TRPV1 to cause neurogenic inflammation, hyperalgesia, and probably pruritus.

TRPV channels communicate with other neuronal receptors, thereby regulating neurogenic inflammation. For example, bradykinin and NGF that are involved in neurogenic inflammation and hyperalgesia via activation of bradykinin-2 receptor (BK2R) and tyrosine kinase (TrkA) receptors, respectively, require expression of TRPV1 on sensory neurons. These effects are mediated, at least in part, by activation of phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2] and phospholipase C (PLC)-γ. Thus activation of different PLC-coupled receptors by individual components of the inflammatory milieu might allow for spatially and quantitatively distinct mechanisms of receptor sensitization, and thereby contribute to intermolecular communication during neurogenic inflammation (162).

In the skin, immunohistochemical analysis indicates that TRPV1 is located in a neurochemically heterogeneous population of small-diameter primary afferent fibers and with small-diameter nerve fibers in the skin of rats and humans (79, 305, 789). These data revealed that TRPV1 is clearly involved in neurogenic inflammation of human skin (78, 789, 792) and can be downregulated by anti-inflammatory agents such as topical calcineurin inhibitors, for example (789).

TRPV1 ion channels have been described on numerous nonneuronal cell types, including human epidermal and hair follicle keratinocytes, dermal mast cells, and dendritic cells (79, 366, 789). Thus TRPV1 activation, in addition to markedly affecting sensory nerves, may also serve as an extraneuronal receptor with several capacities. Thus far, a role for TRPV1 has been observed on keratinocyte proliferation, differentiation, and apoptosis, and probably the release of pruritogenic cytokine mediators from keratinocytes (78, 782).

In clinical dermatology, topical capsaicin treatment has been established. It suppresses histamine-induced itch (930) and is increasingly used to treat pruritus in numerous skin diseases (reviewed in Refs. 70, 882, 954). TRPV1 can be sensitized by other itch receptors such as PAR_2. This can lead to synergistic effects, amplifying the pain and/or itch response.

Together, these findings suggest that TRPV1 may mediate important symptoms of inflammation such as pain, heat, or pruritus and stimulate the release of neuropeptides from specified afferent C-fiber neurons into the environment (149, 867).

B. TRPV2

A second human and rat vanilloid-like receptor (VRL-1, TRPV2) has also been cloned (150). It is 50% identical to TRPV1 and widely expressed in the periphery including the dorsal root ganglia and elicits a high threshold for noxious heat, but does not respond to capsaicin, acid, or moderate heat. Instead, TRPV2 is activated by high temperatures, with a threshold of ~52°C. Within sensory ganglia, TRPV2 is most prominently expressed by a subset of medium- to large-diameter neurons, making it a candidate receptor for transducing high-threshold heat responses in this class of cells. The distribution of TRPV2 transcripts is not restricted to the sensory nervous system (Table 2).

TRPV2 is insensitive to capsaicin but is inhibited in a noncompetitive manner by ruthenium red (37). Like TRPV1, TRPV2 is more permeable to Ca^{2+} than to Na^+ and is outwardly rectifying. It is expressed in medium- to large-diameter neurons of sensory ganglia, but is also present in brain, spinal cord, spleen, and lung. It has been proposed to mediate high-threshold (>52°C) noxious heat sensation, perhaps in the myelinated Aδ fibers, but its presence in nonsensory tissue indicates additional functions, which suggests that this channel is activated by additional stimuli except heat. Thus responses to noxious heat may involve TRPV2 and TRPV1, which together may detect a range of stimulus intensities. They show different distribution and biological functions with different ligand binding (744). A direct or indirect role of TRPV2 during neurogenic inflammation has not yet been verified.

C. TRPV3

Environmental temperature is thought to be directly sensed by neurons through their projections in the skin. Interestingly, in rodents TRPV3 is specifically expressed in skin epidermal keratinocytes and has not been detected in sensory neurons (628). In humans, however, TRPV3 is

also expressed in sensory neurons (776). Cloning and characterization of TRPV3 revealed this receptor to be activated at innocuous temperatures (>33°C) (551, 628). Therefore, heat-activated receptors in keratinocytes, besides neurons, are important for mammalian thermosensation (Table 2).

A crucial question is how keratinocytes and sensory nerves may communicate as temperature sensors. It is well known that keratinocytes contact sensory nerve fibers through membrane-membrane apposition. Therefore, heat-activated TRPV3 may signal from keratinocytes to DRG neurons through direct mediators such as ATP. P2X3, an ATP-gated channel, is present on sensory neurons, and analysis of P2X3 knockout mice shows a strong deficit in the coding of warm temperatures (755). Furthermore, release of ATP from damaged keratinocytes has been shown to cause action potentials in nociceptors via the P2X receptors (172). The precise mechanism and impact of TRPV3 in cutaneous inflammation is still under investigation (628).

D. TRPV4

TRPV4 channels (also known as OTRPC4, VR-OAC, or TRP12) are activated by heat above a threshold temperature of 25°C. Activation requires the intact NH_2-terminal ankyrin repeats. Single TRPV4 channels can be activated by heat in cell-attached patches, but not in cell-free inside-out patches. TRPV4 currents are also activated by cell swelling and the selective ligand 4-phorbol 12,13-didecanoate (4-PDD). Possible ligands also may be arachidonic acid metabolites such as PLA_2 (923).

TRPV4 is widely expressed in mammalian tissues, including heart, brain, kidney, sensory neurons, sympathetic nerves, fat tissue, gut, salivary gland, lung, skin, sweat glands, and the inner ear. In the skin, TRPV4 is expressed by keratinocytes, hair cells, and Merkel cells (303, 304, 484, 582, 824, 941). TRPV4 was the first TRP channel reported to be expressed by endothelial cells from mouse aorta (923). Cooling of peripheral blood vessels therefore induces vasoconstriction, and warming the vessels promotes vasodilatation (538). Therefore, it seems likely that TRPV4 could work as both a cold and a warm receptor. In addition, the temperature sensitivity of TRPV4 may suggest a role during inflammation, e.g., by changing barrier properties that depend on Ca^{2+} influx. TRPV4's role during neurogenic inflammation or vasoregulation during inflammatory processes is anticipated but currently unknown.

E. TRPM8

Hypotheses about a receptor-mediated regulation of cold detection have come from the use of natural products such as menthol and eucalyptol, which elicit a sensation of cold. Fifty years ago it was already demonstrated that menthol shifts activation thresholds of cold-responsive nerve fibers to warmer temperatures, indicating that menthol is likely to "exert its action upon an enzyme, which is concerned in the thermally conditioned regulation of the discharge of the cold receptors" (330). When different cloning approaches were used, a "cold receptor" was independently cloned by various groups and later defined as TRPM8 (528, 627, 880). Originally, TRPM8 was described as a transcriptional marker of transformed prostate epithelia (880).

In contrast to TRPVs, TRPMs can be activated by menthol but not by vanilloids. Thus cold temperatures depolarize neurons by directly activating an excitatory ion channel. As for TRPM8, cooling of sensory neurons below 27°C activates nonselective cation conductances, leading to membrane depolarization and generation of action potentials (627).

TRPM8 is expressed by ~10% of all mouse DRGs, primarily of the small-diameter type. TRPM8 does not appear to be coexpressed with many of the classical nociceptive markers and neuropeptides, which suggests that TRPM8 is a functionally distinct subpopulation (627). Cold temperatures below 28°C evoke robust membrane currents through TRPM8, which saturate near 8°C.

Together, these results provide a molecular explanation for the clinical observation why menthol and eucalyptol evoke a psychophysical sensation of cold, supporting the concept that various TRP channels serve as principle detectors of thermosensation, with some of them additionally involved in pain, pruritus, and inflammation.

F. TRPA1

In addition to TRPM8, another ion channel has recently been described, defined as TRPA1 (ANKTM1). It is activated near 17°C (821). In contrast to TRPM8, TRPA1 is sensitive to icilin (AG-3–5) but insensitive to menthol and eucalyptol (36, 927). Transcripts of TRPA1 are expressed in fewer than 4% of murine sensory neurons. However, the activation of TRPA1 by cold in vivo and its prevalence in sensory nerves is still a matter of debate. From the phylogenetic point of view, TRPA1 has little sequence similarity to the other known mammalian TRP channels, but is most closely related to invertebrate TRP-like channels of the *Drosophila* TRPN subfamily (99). Unlike TRPM8, TRPA1 is found exclusively in nerve cells that also express TRPV1 and neuropeptide markers of neurogenic inflammation and nociception such as SP and CGRP. These data indicate a role of TRPA1 in neurogenic inflammatory circuits. Preliminary studies using the TRPA1-specific agonist icilin in animal and human inflammatory skin diseases, however, are in favor of an important role

of TRPA1 in pain and pruritus over inflammation. TRPA1's role in cutaneous inflammation, maybe by inhibiting proinflammatory stimuli, but this is still under investigation.

VII. ROLE OF PROTEINASE-ACTIVATED RECEPTORS IN CUTANEOUS NEUROGENIC INFLAMMATION AND PRURITUS

The role of proteinase-activated receptors (PARs) in cutaneous inflammation has been recently reviewed in detail (340, 898). As shown for many organs, serine proteases such as thrombin, cathepsin G, tryptase, or trypsin are capable of cleaving PARs to induce widespread inflammation that is characterized by vasodilatation, extravasation of plasma proteins, and infiltration of neutrophils (reviewed in Refs. 205, 899). Similarly, neuropeptides such as CGRP and SP from sensory neurons regulate inflammation. Therefore, proteases may activate PARs on sensory neurons to stimulate release of CGRP and SP, which mediate the inflammatory response. Similar to neuropeptides, natural (tryptase, trypsin) or synthetic agonists (activating peptides, SLIGRL/KV-NH_2) of PAR_2 have widespread proinflammatory effects (233). Tryptase also induces plasma extravasation (547), neutrophil infiltration (812, 899), and stimulates cytokine secretion (351). Moreover, tryptase releasing mast cells can be found in close proximity to PAR_2 expressing cells such as keratinocytes and dermal endothelial cells (351) or C fibers during inflammation (104, 108, 110). Mast cells themselves express PAR_2 and PAR_1 (182), indicating a potential autocrine regulatory role for tryptase in cutaneous inflammation via activating PAR_2.

We were the first to show that sensory neurons express PAR_2, which, when activated, induces neurogenic inflammation (812). In dorsal root ganglia, PAR_2 was detected in >60% of rat sensory neurons, and most of these neurons contained CGRP or SP, respectively. PAR_2 agonists specifically and dose-dependently activated the receptor in cultured sensory neurons and stimulated neuronal CGRP and SP release. Intraplantar injection of a PAR_2 agonist caused marked edema that was abrogated by antagonists of CGRP type 1 and NK1 receptors and by sensory denervation with capsaicin. Moreover, capsaicin pretreatment significantly reduced the magnitude of paw edema to PAR_2 agonists, suggesting a neuronal pathway after PAR_2 activation in vivo. Histological examination of the paw skin indicated that PAR_2 caused a marked edema and infiltration of granulocytes in the dermis. Thus PAR_2 agonists stimulate the release of CGRP and SP from spinal afferent C fibers in the rat paw, and both peptides may result in the extravasation of plasma proteins and fluid but not on infiltration of granulocytes. Potential endogenous agonists in the skin may be trypsin, which is also expressed by endothelial cells (450) or epithelial cells (101) and thus may cleave neuronal PAR_2 in the skin. Another potential ligand is mast cell tryptase (109). In summary, recent knowledge supports an important role for PAR_2 during cutaneous neurogenic inflammation (812) and pain (897) (Fig. 5, Table 2).

Recent findings support a role of neuronal PAR_2 in pruritus (810). These results in humans were confirmed by functional studies in pruritic mouse models (754, 883).

Our knowledge about the underlying mechanisms of PAR-controlled cutaneous inflammation and pruritus is still in its infancy. However, the use of knockout mice as well as better antagonists and human studies may help us to develop new strategies for the treatment of cutaneous disorders that involve PARs, such as atopic dermatitis (810), pruritus (810, 883), contact dermatitis (422, 747), melanoma (518), infection (550), and Netherton syndrome.

VIII. CYTOKINES AND CHEMOKINES AS LIGANDS FOR SKIN SENSORY NERVES

Although cytokines and chemokines compose the largest families of inflammatory mediators, much less is known about their role as ligands and direct activators of sensory nerves. However, the observation that cytokines are capable of inducing pruritus or that cytokine inhibitors exert analgesic capacity even before showing clinically substantial anti-inflammatory effects led to the hypothesis that cytokines may contribute to neurogenic inflammation, pain, and pruritus. Moreover, a cross-talk between neuropeptide receptors with chemokine receptors has recently been proposed as an important link of the neuroimmune axis in the regulation of inflammation and immunity (245, 451, 486, 896, 934, 958).

Ambitious members of "neurophilic" cytokines are IL-1, IL-6, IL-8, and IL-31 (reviewed in Refs. 805, 811). Of note, transgenic mice overexpressing IL-31 released by T cells and macrophages showed a chronic inflammatory skin disease consisting of a T-cell infiltrate and pruritus, similar to atopic dermatitis in humans. IL-31 activates the IL-31 receptor (IL-31R), a heterodimeric receptor composed of the IL-31 receptor A (IL-31RA) subunit, and the oncostatin M receptor (OSMR) subunit. Whether IL-31 exerts its pruritic effects via direct activation of the IL-31R on sensory nerves or indirectly, e.g., via keratinocytes, is currently unknown. The finding that keratinocytes express the IL-31 R suggests that IL-31 may induce pruritus through the induction of a yet unknown keratinocyte-derived mediator, which subsequently activates unmyelinated C fibers in the skin. Therefore, one may speculate that IL-31 is upregulated in pruritic forms of

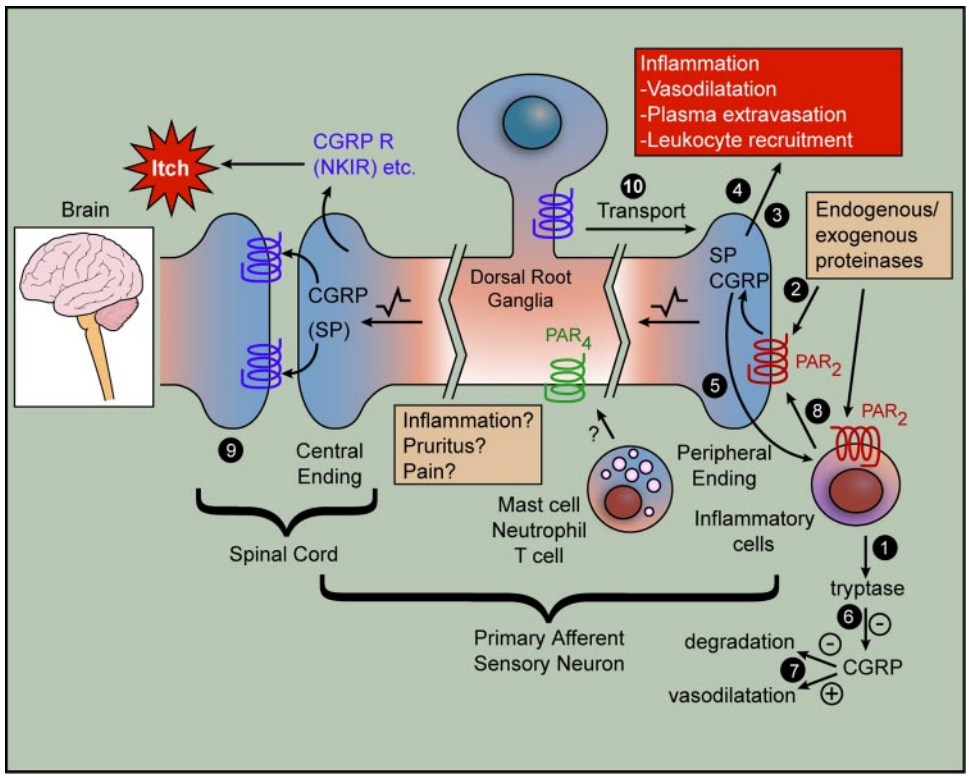

FIG. 5. How proteases talk to sensory nerves in the skin. *1*) Tryptase released from degranulated mast cells activates protease-activated receptor 2 (PAR_2) at the plasma membrane of sensory nerve endings. *2*) Activation of PAR_2 by tryptase, trypsins, kallikreins, or probably exogenous proteinases (bacteria, house-dust mite) stimulates the release of calcitonin gene-related peptide and tachykinins, e.g., substance P from sensory nerve endings. *3*) CGRP interacts with the $CGRP_1$ receptor to induce arteriolar dilation and hyperemia. *4*) SP interacts with the neurokinin-1 receptor (NK1R) on endothelial cells of postcapillary venules to cause gap formation and plasma extravasation. Hyperemia and plasma extravasation cause edema during inflammation. *5*) SP may stimulate degranulation of mast cells, providing a positive feedback mechanism. *6*) Tryptase degrades CGRP and terminates its effects. *7*) CGRP inhibits SP degradation by neutral endopeptidase and also enhances SP release, thereby amplifying the effects. *8*) Mediators from mast cells and other inflammatory cells stimulate the release of vasoactive peptides from sensory nerves and also sensitize nerves. *9*) At the spinal cord level, PAR_2-induced intracellular Ca^{2+} mobilization leads to release of CGRP (and SP) from central nerve endings, thereby activating CGRP receptor and NK1R to transit itch responses to the central nervous system. *10*) During inflammation, PAR_2 may be peripherally transported, thereby increasing receptor density and stimulation.

cutaneous inflammation (68, 781). These findings were recently confirmed in mice. In NC/Nga mice, the expression of cutaneous IL-31 mRNA with scratching behavior was significantly higher than that in NC/Nga mice without scratching behavior. Thus IL-31 may participate in the cause of itch sensation and promote scratching behavior (848, 849). Thus IL-31 may be a new link between the immune and nervous system by regulating inflammation as well as itch (Table 2). IL-31 and the IL-31R are therefore promising targets for the treatment of inflammatory and itchy dermatoses such as atopic dermatitis.

IX. MOLECULAR MECHANISMS REGULATING NEUROGENIC INFLAMMATION

In the preceding section, we described the impact of neuropeptides and their receptors on cutaneous function and inflammation. Recently, the molecular mechanisms that regulate neuroinflammation and terminate these signals have been intensively studied.

The physiological control of cell responses to various inflammatory stimuli requires the regulation at several levels. For example, stimulation of mast cells by SP results in modification of cell function at the transcriptional and posttranscriptional level such as cytokine synthesis or secretion. Receptor regulation delineates a further possibility to control cell function. On the receptor level, we are faced with various possibilities that regulate receptor-ligand interactions, such as receptor number, receptor affinity, receptor desensitization, uncoupling of receptors from their ligands, endocytosis, receptor recycling, or lysosomal trafficking. Moreover, signal amplification may occur through activation of specific second messenger pathways. Thus dysregulation of these processes may result in disease or uncontrolled inflammation. For example, abnormalities in the release or degradation of neuropeptides, in receptor regulation, or during signal transduction may result in neurogenic inflammation, vascular permeability, hyperalgesia, analgesia, or pruritus.

A. Synthesis, Posttranslational Processing, and Secretion of Neuropeptides

Biologically active neuropeptides can be generated in many ways. In most cases, neuropeptides are derived from unique genes, although in some cases, identical peptides can arise from different genes. At the transcriptional level of certain neuropeptide genes such as the tachykinin gene, alternative RNA splicing results in the formation of different RNA transcripts and thus different peptides for the same gene. Finally, different neuropeptides may be formed by alterations in posttranslational processing of peptide precursors. Like other regulatory peptides, neuropeptides are initially synthesized as an inactive precursor protein that is converted to a biologically active form by posttranslational modifications. Proteins that are destined for secretion, such as the biologically active neuropeptides, are sorted into secretory granules, in the "regulated" pathway. Proteins that are destined for the plasma membrane, such as neuropeptide receptors and NEP, enter the "constitutive" pathway, enabling a rapid and regulated transport to the cell surface. Final modifications of transported neuropeptides such as POMC gene peptides, for example, occur within the secretory granules (253). These modifications include the cleavage at dibasic and monobasic residues by endopeptidases, such as prohormone convertases. Cleavage of these precursors within secretory granules ensures that all of the neuropeptides will be released into the extracellular fluid. However, not all of the secreted neuropeptides are immediately biologically active and require further cleavage by extracellular peptidases (561). Different peptides can result from the transcription of distinctly different genes. However, the same or similar peptides may form from different genes that are differentially expressed throughout the body.

B. Coexistence of Neurotransmitters

The extensive use of immunocytochemistry to localize peptides has revealed that individual neurons coexpress and presumably cosecrete multiple neuropeptides (reviewed in Refs. 44, 685). Furthermore, both peptide and nonpeptide neurotransmitters are invariably coexpressed. For example, CGRP is often colocalized with SP or somatostatin, whereas SP is rarely colocalized with somatostatin, and VIP is rarely colocalized with other neuropeptides but is preferentially colocalized with nonpeptide neurotransmitters such as catecholamines, ACh, or NO, indicating the preferred localization of VIP in autonomic skin fibers. In summary, the physiological relevance of the release of various neuropeptides from one neuron is still unclear, although neuropeptides may increase and/or amplify the function of simultaneously secreted neurotransmitters.

C. Mechanisms Regulating Neuropeptide Receptor Function

Neuropeptide receptors are expressed on central terminals of sensory nerves and thereby transmit important stimuli to the CNS, such as pain, burning, and pruritus. Additionally, many cutaneous cells, endothelial cells, as well as immune cells express neuropeptide receptors, which are involved in inflammation and immunomodulation. Most of the neuropeptide receptors belong to the GPCR family of receptors. Thus the ability of skin cells to respond to neuropeptides requires the presence of GPCRs that are appropriately located at the plasma membrane, where they can interact with agonists from the extracellular fluid. In contrast, neurotrophin receptors transduce their signals as tyrosine kinase receptors (e.g., trkA, trkB, and others). For example, neurotransmitters can exert their effects via GPCRs, as in adrenergic receptors, or via ion channels, as in nicotinergic ACh receptors. In addition, besides binding to their high-affinity receptors, certain peptides are capable of stimulating not only neuropeptide receptors, but also ion channels. This has been demonstrated for endogenous molecules such as anandamide or bradykinin, for instance, both of which induce activation of the TRPV1 receptor (40). Finally, certain GPCRs or GPCRs closely associated with ion channels may activate or inactivate each other, a mechanism known as heterologous sensitization/desensitization.

This review focuses on the molecular and cellular mechanisms regulating GPCR function with respect to the skin. For further general aspects and other receptor subfamilies, other excellent recent reviews should be consulted (829).

In general, signal transduction of GPCRs is rapidly terminated by phosphorylation of the agonist-occupied receptor by G protein-coupled receptor kinases (GRKs). One of the first signals after binding of the agonist is the uncoupling of the receptor from the heterotrimeric G proteins which leads to desensitization of the receptor (905). Often, but not always, the desensitized receptors are internalized as a receptor-ligand complex. During the intracellular trafficking, vesicular acidification induces the dissociation of the ligand from the receptor. Hence, the ligand is sorted into lysosomal degradation and the receptor is dephosphorylated and recycled to the cell surface; the cells are resensitized (682).

Few neuropeptide receptors are regulated different from the above-described mechanism. For example, one subtype of the receptors for somatostatin, sst2, which is expressed by human monocytes, macrophages, and dendritic cells (179), internalizes after stimulation with SST-14, but the ligand is recycled to the cell surface as intact SST-14 (358). The angiotensin II type 1A receptor (AT2R1A), a GPCR expressed by mast cells and leukocytes (646), also does not transport the ligand into lyso-

somal degradation (178, 443). After agonist stimulation, AT2R1A and the NK1R are found sequestrated for hours when expressed in heterologous expression systems (594).

Differences in the mechanisms of desensitization and resensitization are also under the control of the ligand concentration, suggesting the important role of receptor trafficking in regulating skin function (682), since dysregulation of those receptors causes disease in the organism (43).

1. *Agonist removal by neuropeptide-degrading enzymes*

Recent studies indicate that a variety of peptidases play an important role in the control of cutaneous neurogenic inflammation. For example, the metalloendopeptidases ACE and ECE are capable of degrading the tachykinin SP, bradykinin, and angiotensin, whereas NEP additionally cleaves NKA, NKB, VIP, (PACAP-27), ANP, SST-14, and endothelins (390). PACAP-38 is not degraded by NEP (237). Recently, cell surface-located serine dipeptidyl peptidase IV was found to inactivate PACAP-38 in vivo and in vitro (964). Thus endopeptidases tightly regulate the capability of neuropeptides to activate their cognitive receptors on the cell membrane.

ACE is predominantly found on the luminal side of vascular endothelium, which limits its range of actions predominantly to vascular responses (vasodilatation, plasma extravasation, leukocyte-endothelium adhesion) (136). In the skin, both NEP and ACE have been identified in vascular endothelial cells (740), skin fibroblasts (389), and keratinocytes (565, 602).

Conclusive evidence for the role of ACE and NEP in modulating a number of biological processes derives from studies of mice in which the gene for ACE or NEP has been deleted by homologous recombination. Deletion of NEP in $NEP^{(-/-)}$ mice renders them sensitive to endotoxic shock (492). In the skin, $NEP^{(-/-)}$ mice showed an increased constitutive plasma extravasation from postcapillary venules in several tissues including skin. Moreover, in a model of experimentally induced contact dermatitis of the ear, $NEP^{(-/-)}$ mice demonstrated a significant increase of plasma extravasation and cutaneous inflammation that peaked after 6 h (740, 804). This leakage was attenuated by injection of recombinant NEP, or antagonists against NK1R and BK2-R, respectively. Thus inhibition or genetic deletion of NEP impairs the degradation of the proinflammatory mediator bradykinin and SP that results in an increased vasodilatation and plasma extravasation mediated by NK1R and BK2-R (492).

NK1R and NEP are often coexpressed by the same target cell. Despite the ~10,000-fold lower affinity of SP to NEP compared with that to NK1R, NEP can efficiently inhibit NK1R signaling, if expressed at high concentrations and in the vicinity of NK1R at the cell surface (600). Once neuropeptides are activated and released on target cells, peptidases may be important for degrading these molecules in the extracellular space.

Recently, splice variants of NEP and ECE have been characterized. Interestingly, these variants are partially localized intracellularly, inside the endo- and exocytotic pathways of these cells. This observation suggests that both transmembrane as well as intracellular peptidase activity may play a major regulatory function in receptor resensitization (561, 562).

Although the level of endopeptidase expression is important because of its activity on skin cells, its regulation is not well characterized. So far, NEP activity is known to increase after stimulation with proinflammatory cytokines (449), by agents that increase the intracellular cAMP level (284), and glucocorticoids that also downregulate NK1R expression (89, 90). Moreover, both NEP and ACE expression are upregulated during wound healing (797). In summary, these findings imply that upregulation of endopeptidases is an important mechanism of limiting proinflammatory effects of degradable neuropeptides by reducing their pericellular concentrations close to the receptor. Thus downregulation of neuropeptide degrading enzymes, on the other hand, may result in uncontrolled function of neuropeptides and disease.

2. *Receptor desensitization and uncoupling of receptor from G proteins*

A characteristic of responses to agonists for GPCRs such as the NK or CGRP receptors, for example, is the rapid attenuation of the signaling after stimulation. One of the first events after activation of a receptor is the termination of intracellular signal transduction pathways. The signal transduction is functionally blocked by phosphorylation of the receptor by G protein receptor kinases (GPRKs). There exist at least six different GPRKs that have the characteristic of only phosphorylating agonist-occupied receptors. The process is defined as homologous desensitization. The NK1R, for example, was shown to be associated with GRK-2 and -3 (462, 526). GPRK-mediated phosphorylation of a GPCR is in general coupled with the translocation of β-arrestin from the cytosol to the plasma membrane and binding of β-arrestin at the GPCR-phosphorylated receptor. β-Arrestins are soluble cytoplasmic proteins that interact with phosphorylated GPCRs, receptor kinases, and other important molecules such as clathrin. So far, of the three known β-arrestins, β-arrestin-1 and -2 appear to be the most important for desensitization of neuropeptide receptors. Studies in live cell experiments demonstrated that β-arrestin-1 is found colocalized with NK1R 1 min after stimulation of the receptor. Although important, the role of GRKs and arrestins for the regulation of physiological and pathophys-

iological neuropeptide-mediated events in the skin and immune cells involved in cutaneous inflammation is still poorly understood.

"Resensitization," on the other hand, means the ability of the neuropeptide receptor to recover after the response to the corresponding agonist. Therefore, neuropeptide receptors have to be dephosphorylated. Normally, receptor dephosphorylation takes place during the intracellular trafficking process of the neuropeptide receptor. The extent of resensitization is affected by the duration of exposure and the concentration of the ligand, suggesting an important regulatory role of the process during cell function. Recently, we demonstrated that NK1R stimulated with 1 nM SP resensitized in <5 min, whereas stimulation with 10 nM SP induced intracellular sequestration of the receptor, and resensitization took place in >2 h (682) (Figs. 2 and 3). From this one may speculate that under normal circumstances, the resensitization processes of NK1R after SP stimulation are tightly regulated in skin cells on endothelial cells and keratinocytes, for example. However, the mechanisms affect resensitization-mediated processes in cutaneous cells under pathophysiological conditions such as inflammation and wound healing.

Remarkably, continued stimulation with agonists could result in diminished recycling of the receptors to the cell surface, defined as "downregulation." Downregulation of receptors is thought to be protective for cells against chronic exposure. For a few GPCRs, however, chronic exposure upregulated surface-located receptors (356). In human endothelial cells, internalization after ligand binding reduced the number of NK1Rs on the cell surface and thus may participate in the desensitization and resensitization of the inflammatory response to SP (101). Because plasma leakage of postcapillary venules normally is transient and undergoes rapid desensitization, e.g., during acute contact dermatitis, this mechanism is likely to play a role in the regulation of plasma extravasation of postcapillary venules (wheal, edema, flare) during cutaneous inflammation.

3. Receptor endocytosis, trafficking, and recycling

In general, neuropeptide-induced endocytosis of GPCRs is important for resensitization of peptide signaling because the responsiveness of the target cells is critically dependent on the subcellular distribution of the receptor. Although endocytosis of neuropeptide receptors and subsequent intracellular sorting are critically important cellular processes, the mechanism and function of internalization and subsequent trafficking differs between neuropeptide receptors (reviewed in Refs. 83, 85, 282, 475, 535, 876).

For example, SST-14, which is important for regulating keratinocyte growth and proliferation, induces clathrin-mediated endocytosis of the sst3 receptor in various cells. Subsequently, SST-14 and sst3 internalize into early endosomes. After endosomal acidification which results in uncoupling of the ligand and receptor, SST-14 is degraded in lysosomes while sst3 immediately recycles to the cell surface where it may respond again to SST-14 stimulation. Similar to sst3, stimulation of NK1R or the AT1AR induces clathrin-mediated endocytosis. In contrast to the sst3, however, the NK1R and AT1AR sequestrate for hours until the receptor recycles to the cell surface where cells become resensitized (178, 594, 728).

Resensitization of PARs is different from the described mechanisms of neuropeptide receptors. Proteolytic cleavage of the NH_2-terminal end of the receptor irreversibly activates the PARs. Activated PARs are transported into lysosomal degradation. The cells resensitize, by transport stored receptors from the post-Golgi network to the cell surface (84, 683) (Fig. 6). In general, recycling of internalized neuropeptide receptors includes dissociation of receptors from their ligands and receptor dephosphorylation, both of which contribute to resensitization of cellular responses. Thus the main mechanism of desensitization of many neuropeptide receptors is uncoupling from G proteins that involves receptor phosphorylation and association with β-arrestins.

Finally, SP activation of NK1R stimulates the formation of a scaffolding complex consisting of the internalized receptor, further β-arrestins, src, and ERK1/2. Inhibition of complex formation by expressing dominant neg-

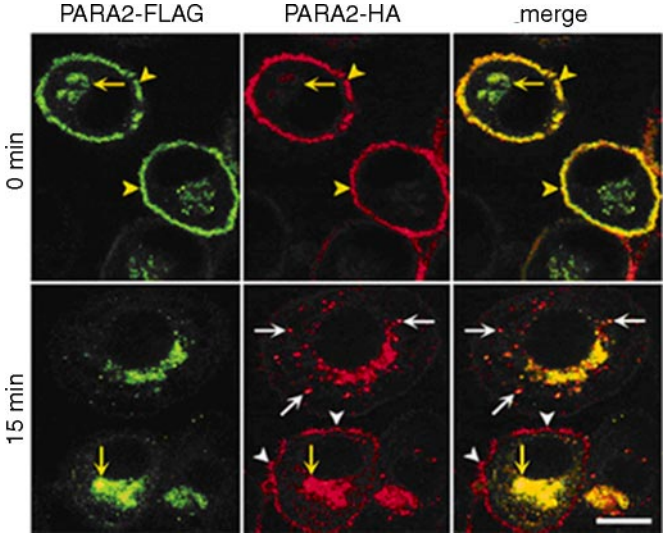

FIG. 6. Localization of PAR_2 with Flag and HA11 antibodies. Cells were incubated with 10 nM trypsin for 0 (*A*) or 15 (*B*) min and processed for immunofluorescence. *Right*: superimposition of images in the same row. In unstimulated cells (*A*), Flag and HA11 colocalized at the plasma membrane (yellow arrowheads) and the Golgi apparatus (yellow arrows). After trypsin, Flag was cleared from the plasma membrane. HA11 was detected in vesicles that did not contain Flag (white arrows) and at the plasma membrane (white arrowheads). Scale bar = 10 μm. [From Roosterman et al. (683), used with permission.]

ative dynamin inhibits both SP-stimulated endocytosis of the NK1R and activation of ERK1/2, which is required for the proliferative and antiapoptotic effects of SP, for example, on HEK293 and COS-7 cells (599, 866). These results indicate that a β-arrestin-containing complex facilitates the proliferative and antiapoptotic effects of SP (184) (Fig. 7). Thus understanding the intracellular events after neuropeptide receptor regulation may allow us to develop new strategies for the treatment of skin diseases that involve neuropeptide receptors.

4. Receptor downregulation

Receptor downregulation is a further mechanism to control neuropeptide-induced cell stimulation and is characterized by a decrease in the total number of receptors in a cell. It is caused by long-term exposure of the cell to the neuropeptide over hours or days. The simultaneous recovery of the cell from receptor downregulation is rather slow. Because other efficient mechanisms exist to inactivate neuropeptides within the extracellular fluid in seconds, this mechanism is probably rare in skin cells under physiological conditions. However, receptor downregulation may be an important mechanism under pathophysiological circumstances, when there is continuous production of a neuropeptide, e.g., during inflammation or continuous release of neuropeptides from sensory nerves, or during long-term administration of receptor agonists for therapeutic reasons. Then, receptor downregulation may be responsible for inducing tolerance or tachyphylaxis against neuropeptides, as has been shown for somatostatin and octreotide, for example.

Possible mechanisms controlling receptor downregulation include enhanced degradation, reduced synthesis of neuropeptide and neurotransmitter receptors, or sequestration of the receptor induced by stimulation with synthetic agonists to neuropeptides or neurotransmitters. Most knowledge in this field derives from studies of the β2-adrenergic receptor (β2-AR), a receptor involved in regulating sweating and keratinocyte function, for example (653, 713). Studies in keratinocytes demonstrate that β-adrenergic receptor activation delays wound healing via a protein phosphatase 2A (PP2A)-dependent mechanism (653). Moreover, agonist-dependent PKA-independent pathways and PKA-dependent heterologous pathways may be involved in β2-AR signaling (963). Thus long-term agonist exposure and subsequent G protein coupling may result in distinctive phosphorylation patterns or a particular receptor confirmation that exposes specific lysosomal targeting sequences. These sequences may interact with the machinery in the sorting endosome and target the receptor away from the recycling pathway towards degradation (Fig. 8).

5. Decreased receptor synthesis

Another important component of receptor downregulation is decreased receptor synthesis, which may be a result of reduced gene transcription or of posttranslational modifications such as mRNA destabilization. This has been shown for several neuropeptide/neurotransmit-

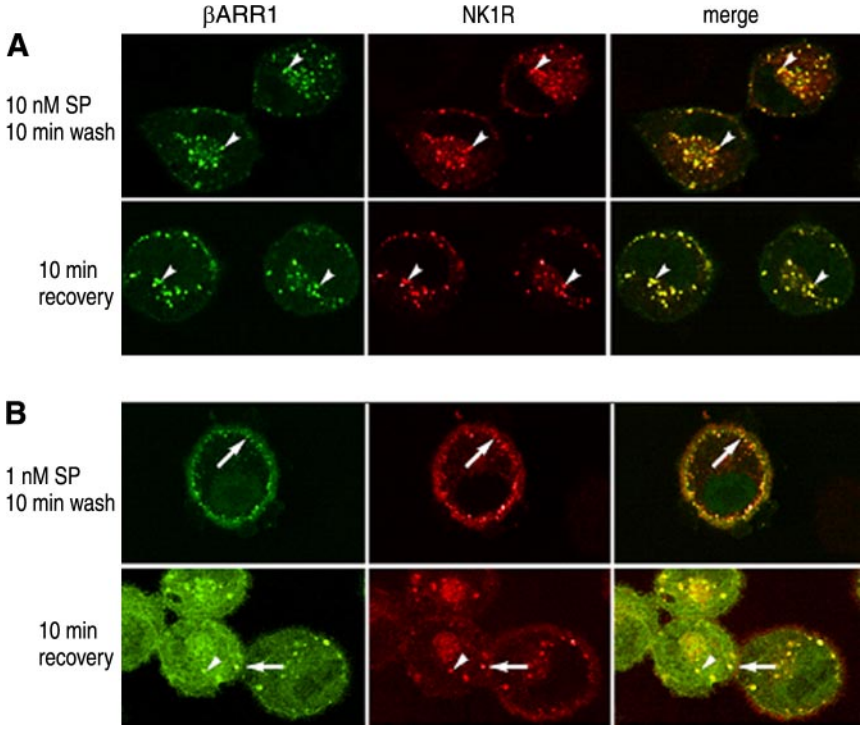

FIG. 7. SP-induced trafficking of β-arrestin 1-green fluorescent protein (GFP)-coupled NK1R. KNRK-NK1R cells were incubated with 10 nM SP (*A*) or 1 nM SP (*B*) for 10 min at 37°C, washed, and incubated for 0–60 min at 37°C. Cells were fixed, and the NK1R was localized by immunofluorescence by using anti-FLAG and β-arrestin 1 (βARR1) by GFP. Stimulation with 10 nM SP induced endocytosis of βARR1 and the NK1R into superficial and perinuclear endosomes for at least 60 min. After 60 min, there was some return of βARR1 to the cytosol. Stimulation with 1 nM SP induced endocytosis of βARR1 and the NK1R into superficial endosomes that moved to a perinuclear location only at later time points. However, βARR1 was minimally depleated from the cytosol. Within 30 min of recovery, the NK1R was detected at the cell surface. Scale bar = 10 μm. [From Roosterman et al. (682), copyright The American Society for Biochemistry and Molecular Biology.]

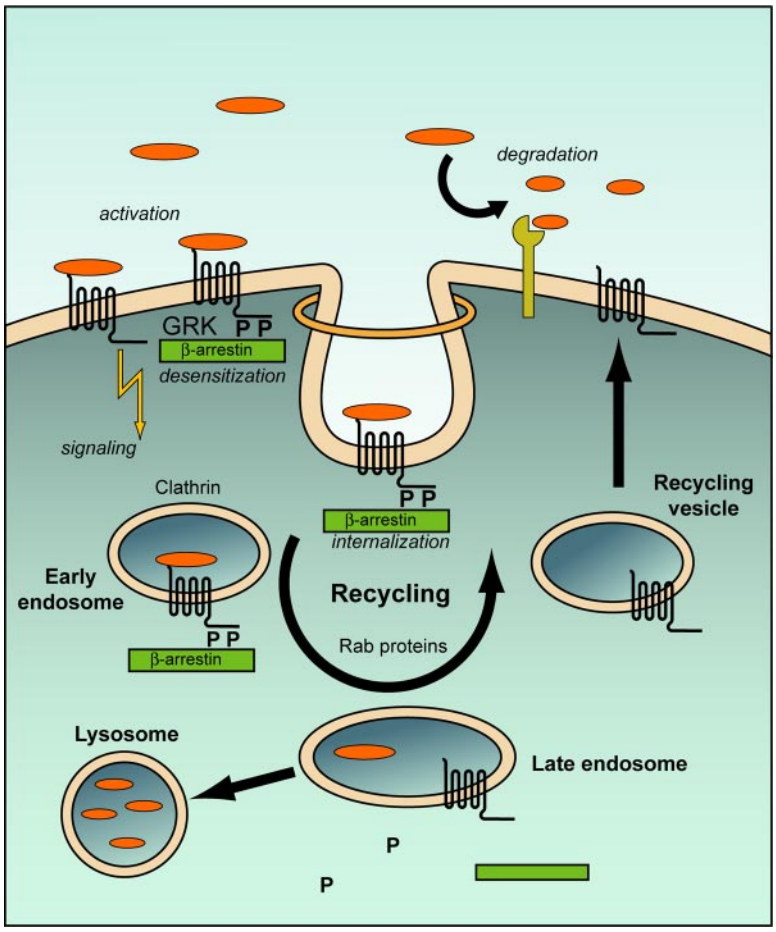

FIG. 8. Intracellular trafficking of a neuropeptide receptor (exemplified by neurokinin-1 receptor) and associated proteins in various cells and nerves. In the soma, agonist binding is followed by receptor phosphorylation by G protein-coupled receptor kinases (GRKs), interaction with β-arrestins, followed uncoupling from G proteins, which mediate receptor desensitization. The ligand-receptor complex, possibly associated with β-arrestin (a clathrin adaptor), internalizes via clathrin into vesicles that soon shed their clathrin coat and become early endosomes. Dynamin may mediate endosome formation. Ligand and receptor dissociate in an acidified perinuclear compartment by poorly understood mechanisms. Rab proteins are involved in the sorting process of a neuropeptide receptor. Endosomal phosphatases may dephosphorylate the receptor, allowing dissociation of β-arrestins. The ligand is degraded, whereas the receptor recycles to the plasma membrane, where it can be resensitized by the neuropeptide ligand. Thus resensitization requires internalization, processing, and recycling of the neuropeptide receptor. In sensory nerves, receptor desensitization and endocytosis may proceed by a similar mechanism. However, different trafficking mechanisms of the NK1R can be observed in the neurite compared with the soma.

ter receptors such as the β2-AR, m1AChR, NK1R, or endothelin B (ET_B) receptor, for example (227), all of which are crucially involved in skin function, pruritus, and/or immunomodulation. The cAMP response element modulator (CREM) appears to have an important modulatory role for some receptors on the transcriptional level. Finally, destabilization of mRNA for GPCRs is strongly dependent on cAMP generation and PKA activation. The involvement of PKA suggests phosphorylation of factors such as GPCR-binding proteins, which subsequently degrade specific receptor mRNA or induce transcription and translation of such factors (Fig. 8).

In summary, a deeper understanding about the molecular mechanisms regulating neuropeptide and neurotransmitter receptor generation, activation, and downmodulation in cutaneous cells may help us to develop novel strategies for the treatment of several skin diseases that involve the neuronal system and neuromediators.

X. ROLE OF THE NERVOUS SYSTEM IN SKIN PATHOPHYSIOLOGY

Cutaneous nerves are closely associated with most target cells and structures in the skin including Langerhans cells, keratinocytes, Merkel cells, mast cells, blood vessels, fibroblasts, and skin appendages such as hair follicles and eccrine and sebaceous glands. However, our knowledge about the exact role of neuropetides in the regulation of inflammatory and immune responses in the skin is far from complete. A number of human disorders appear to have a significant neurogenic component, such as inflammatory bowel disease, asthma, ophthalmic herpes virus infections, multiple sclerosis, and arthritis (22, 816). In the skin, there is evidence that the cutaneous nervous system contributes to the pathogenesis of urticaria, psoriasis, atopic dermatitis, contact dermatitis, hypersensitivity reactions, erythromelalgia, prurigo, pruritus, and wound healing (22, 805, 811). Moreover, neuropeptides are involved in the pathophysiology of pruritus as well as in UV light-induced immunomodulation (258).

A. Urticaria

The ability of neuropeptides to activate human mast cells and induce urticaria has been appreciated for a number of years (165). Investigators have demonstrated that neurokinins such as SP are capable of binding to and directly activating mast cells in vitro and triggering the

release of immediate hypersensitivity mediators such as histamine (623). Neuropeptides may also be responsible for the release of mast cell cytokines such as TNF-α which may mediate late-phase inflammatory responses (23).

SP and CGRP have been shown to exert cutaneous responses in chronic urticaria (86). Interestingly, chronic idiopathic urticaria and, to a lesser extent, pressure urticaria showed enhanced SP- and CGRP-induced wheal and flare reactions. CGRP elicited an immediate wheal and flare response, followed by prolonged erythema. Histamine-1 receptor antagonists partially affected wheal and flare reactions to SP and only the flare response induced by CGRP. However, this effect was more pronounced in urticaria patients.

As described above, certain TRP ion channels are expressed by sensory nerves as well as by mast cells. Some of these are temperature-sensing receptors responding to cold and heat. One of the yet unproven but intriguing ideas is that certain "heat" or "cold" receptors may be involved in the pathophysiology of heat or cold urticaria, respectively. Verification of this hypothesis would enable us to develop new strategies for the treatment of these therapeutically difficult diseases.

Together, these results strongly indicate that the skin nervous system directly, or in conjunction with mast cells, participates in the pathophysiology of acute and chronic urticaria.

B. Psoriasis

A neurogenic component for the pathophysiology of psoriasis is suggested both by clinical and experimental studies (59, 244, 572, 573). Clinically, psoriatic lesions often have a symmetrical distribution in regions that are traumatized. The so-called Koebner phenomenon in psoriasis may be initiated by the release of proinflammatory neuropeptides in the traumatized human skin (243). Investigators have also reported increased levels of neuropeptides and sensory nerves in psoriatic skin lesions, and capsaicin, a chemical that depletes neuropeptides from nerve endings, has been reported to have some therapeutic value in clearing lesions (59, 244). Increased concentrations or immunoreactivity for several neuropeptides have been observed in lesional skin of patients with psoriasis (10, 154, 572, 573, 643, 809). Interestingly, an increase of both VIP- and CGRP-immunoreactive fibers was observed in lesional skin of patients with atopic dermatitis of the "high-stress" group. However, no correlation with SP (pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors) was found (323). VIP and CGRP expression were also elevated in nerve fibers of rats stressed by immobilization or in the skin of psoriasis patients (10, 423). Additionally, PACAP-38 was shown to be increased in lesional skin of psoriasis patients (809). Finally, SST or SST analogs have been used for the treatment of psoriasis (520). In patients with psoriasis, the number of somatostatin- and factor XIIIa-positive dendritic cells was significantly reduced during topical treatment with clobetasol propionate or calcipotriol. The reduction rate of the somatostatin-positive cells during treatment supports the idea that SST might play a role during the clearing process of psoriasis (851, 852).

Recent evidence suggests a role of NGF as a mediator of inflammatory responses during psoriasis. In both nonlesional and lesional human psoriatic skin, immunostaining for trkA and p75NTR was reduced compared with control skin (128). Moreover, reduced staining for trkA was found after UVB irradiation as well as for p75NTR, in epidermal nerve fibers of lesional psoriatic skin, and in dermal fibers of both nonlesional and lesional psoriatic skin. UVB irradiation of normal skin led to a statistically significant decrease in the p75NTR-immunopositive fine nerve fibers in the epidermis at 48 h after irradiation, whereas there was no significant reduction of dermal p75NTR immunoreactivity.

C. Atopic Dermatitis

In acute as well as lichenified lesions of atopic dermatitis, increased staining of cutaneous nerves or concentrations of neuropeptides was observed (265, 299, 377, 418, 609, 642, 826, 874, 886). Furthermore, characteristics of the triple response (erythema, wheal, flare) of "neurogenic inflammation" as well as pruritus have been observed after injection of neuropeptides into human skin (333, 335).

In patients with atopic dermatitis, tachykinin receptors were detected on blood vessels and keratinocytes by autoradiography (539, 793). Additionally, NK1R expression on endothelial cells was diminished after UVA irradiation, whereas NK1R expression on keratinocytes was unchanged, indicating a differential regulation of this receptor in different target cells by UV light and during cutaneous inflammation. Of note, the expression of neurokinin receptors was modulated after UVA irradiation in patients with atopic dermatitis (793).

Moreover, SP may have a modulatory effect on proliferation and cytokine mRNA expression of peripheral blood mononuclear cells in response to dust mites (*Dermatophagoides farinae* Der f) in atopic dermatitis patients. SP promoted the Der f-induced proliferation and upregulated IL-10 mRNA expression while downregulating IL-5 mRNA expression. Proliferation in high responders was associated with upregulation of IL-2 mRNA expression and induction of IL-5 mRNA expression, suggesting that SP modifies immune responses of T cells to Der

f by promoting proliferation and altering cytokine profiles, which may influence clinical manifestations of atopic dermatitis (953) especially considering the elevated levels of SP in atopic skin (377, 418).

SP and VIP may have opposing effects on the release of TH1- and TH2-related cytokines in atopic dermatitis. Although SP increased both the TH2 cytokine IL-4 and the TH1 cytokine IFN-γ, the release of both cytokines was inhibited by VIP in vitro. These data suggest a non-TH1/TH2 modulating effect of these neuropeptides on T cells which awaits further confirmation in in vivo experiments.

Intracutaneous injection of VIP led to dose-dependent pruritus as well as wheal and flare in normal and atopic skin. Furthermore, an increase in blood flow was measured after combined VIP and ACh administration in patients suffering from acute atopic dermatitis, whereas flare area and plasma extravasation were significantly reduced after single VIP and combined VIP and ACh injections, respectively (690, 691). Recent in vivo studies in human skin suggest that active vasodilatation depends solely on functional cholinergic fibers, but not on ACh itself (52). Downregulation of VIP receptor expression measured by immunohistochemistry of atopic skin and elevated VIP serum levels in atopic patients further indicate a role of this receptor in atopic dermatitis (299, 885).

The role of POMC peptides in the pathogenesis of atopic dermatitis is supported by the in vitro observation that α-MSH modulates IgE production and the finding of increased levels of POMC peptides in the skin of patients with atopic dermatitis (693, 694). Bigliardi et al. (67) investigated the role of β-endorphin in the pathophysiology of atopic dermatitis. They found immunoreactivity for β-endorphin in keratinocytes and unmyelinated sensory nerve fibers by immunofluorescence. β-Endorphin-positive keratinocytes were clustered around μ-opioid receptor-positive nerves (67). Moreover, μ-opioid receptor expression was diminished in skin biopsies from patients with atopic dermatitis. The receptor was internalized in the keratinocytes of those patients, suggesting agonist-induced activation and trafficking in these cells (66). On the basis of observations that morphine and endorphins are involved in the transmission of itch in sensory nerves, one may speculate that the endorphin/μ-opioid receptor system may be involved in inflammatory and pruritic processes of atopic dermatitis (787).

However, these types of preliminary studies support but do not prove the potential involvement of the neurological system in inflammatory skin diseases. Topical application of a tricyclic antidepressant that exerts its effects via mast cells and axon-reflex mechanisms was tested in patients with atopic dermatitis. Doxepin was effective in the inhibition of histamine-induced and SP-mediated cutaneous responses but also evoked sedative effects in some patients.

Recent studies suggest that neurotrophins may participate in the pathophysiology of atopic dermatitis. NGF and its high- and low-affinity receptor (trkA, TrkB) are upregulated in the skin of atopic dermatitis patients. Recent evidence indicates that NGF supports nerve sprouting and may thereby modulate itch perception in the inflamed skin as well as neurogenic inflammation.

In atopic dermatitis, enhanced expression and release of NGF was described in mast cells and keratinocytes, less in fibroblasts (297). Plasma levels of NGF were also increased in those patients. Interestingly, NGF induced histamine and tryptase release from the mast cell line HMC-I. This finding, together with the known effects on keratinocytes, may lead one to speculate that NGF may regulate mast cell-nerve and keratinocyte-nerve interactions in the skin during atopic dermatitis.

In human keratinocytes, NT-4 production was induced by IFN-γ in vitro, and NT-4 expression was increased in atopic dermatitis (295). Immunohistochemistry also revealed NT-4 staining in the epidermal layer and NT-3 staining in the dermal compartment. However, NT-4 but not NT-3 expression was markedly increased in IFN-γ-injected skin. Prurigo lesions of atopic dermatitis on skin were characterized by intense epidermal staining for neurotrophin-4, suggesting a pathophysiological role for this neurotrophin in atopic dermatitis and prurigo.

D. Immediate and Delayed-Type Hypersensitivity

Neuropeptides are obviously involved in the regulation of epidermal antigen presentation. The major antigen-presenting cells of the epidermis, Langerhans cells (LC), make up ~3% of the epidermal cell population. In immunohistochemical studies in rats, sensory nerve fibers were found in close anatomical association with LCs that were able to synthesize the neuronal marker PGP 9.5 after cutaneous denervation (354, 796). So far, immunoreactivity for CGRP, VIP, SP, and neurotensin have been detected associated with LC by cytofluorometry.

Neuropeptides appear to play a role in both immediate and delayed-type hypersensitivity reactions in the skin. SP has been demonstrated to participate in or modulate immediate-type skin hypersensitivity reactions and is recognized as one of the main neuropeptides responsible for the "wheal and flare" reaction characterized by erythema, pain, and swelling. Delayed-type hypersensitivity (DTH) and contact hypersensitivity (CHS) are delayed T-cell-mediated immune reactions occurring in the skin after a first injection (as in DTH) or contact sensitization (as in CHS) with an antigen, followed by a second contact with the hapten (elicitation). Because pretreatment of the skin with capsaicin enhances CHS at the site of treatment, it was suggested that capsaicin-sensitive neurons modulate this reaction via the release of neuropeptides, both in humans and rats (263, 348).

Early studies showing that histamine is involved in DTH reactions implicate an involvement of SP in allergic skin reactions, because SP induces histamine release by rat connective tissue-type mast cells in a cell-specific way in vitro (222, 246). SP released from cutaneous nerves acts as an adjuvant, raising the immunogenicity of epicutaneously applied haptens (581, 822). Similarly, an inhibitor of SP diminishes CHS and DTH responses in human studies when injected at the site of allergen contact (915). SP is capable of inducing both mast cell TNF-α mRNA and secreted TNF-α activity (23). This effect was not generalized because SP did not affect mast cell IL-3 and IL-6 production, thereby supporting the idea of a crucial role of SP in directly activating mast cells to produce cytokines such as TNF-α that may mediate mast cell-induced delayed inflammatory responses in the skin. Finally, SP agonists promoted CHS induction and prevented tolerance when hapten was painted on skin exposed to acute, low-dose UVB radiation. Thus SP agonists enhanced the generation of hapten-specific immunogenic signals from the dermis, suggesting that SP is a mediator that promotes the induction of CHS within normal skin (581). These results strongly indicate that exogenous SP agonists can prevent impaired CHS and tolerance after UVB irradiation, although the susceptibility of native SP to local neuropeptidases (e.g., NEP, ECE-1) renders the neuropeptide unable to prevent the deleterious effects of UVB radiation on cutaneous immunity (740).

Other neuropeptides appear to have a suppressive effect on hypersensitivity reactions in the skin. CGRP, which is released by sensory neurons during the elicitation phase of CHS (264), appears to be capable of suppressing DTH reactions and CHS reactions in mice. This ability seems to be mediated through interactions with LC, as has been shown in mice and humans (348, 423). Using a mouse model of contact hypersensitivity, Garssen et al. (258) showed that in sensory-nerve-depleted mice, exposure to UV light failed to inhibit contact hypersensitivity, indicating that neuropeptides are involved in this process. However, these authors did not analyze specific peptides. Since a general approach was used (depletion of all peptides, i.e., pro- and anti-inflammatory by denervation), the underlying mechanism is not understood. Moreover, pretreatment of mice with selective antagonists to CGRP and tachykinins further indicated that predominantly CGRP rather than tachykinins were involved in UV light-induced systemic immunosuppression. One explanation for this effect may be that CGRP reduces the density of LC and the release of TNF-α from mast cells, which impairs induction of contact hypersensitivities (580). In a mouse model, CGRP significantly inhibited antigen presentation to an antigen-specific T-cell hybridoma, DTH or CHS assays, as shown by mixed epidermal cell/lymphocyte reactions (30, 348). The effect of CGRP on murine LC is probably mediated via a specific CGRP receptor, leading to intracellular cAMP increase (32). One possible mechanism for the decreased capacity of LC to present antigens may be the downregulatory role of CGRP on B7–2 expression, an important regulatory molecule during antigen presentation. Simultaneously, IL-10 may be upregulated by CGRP (870).

α-MSH is one of the most powerful neurohormones in terms of its ability to modify CHS reactions (281). α-MSH inhibits both the sensitization and elicitation phase of CHS and induces hapten-specific tolerance in mice (281). This inhibition is at least in part mediated by the inhibition of accessory signals on human antigen presenting cells and the induction of the immunosuppressive cytokine IL-10 that has been shown to inhibit the elicitation phase of CHS and induce tolerance (63). Because anti-IL-10 antibodies were able to specifically block this effect, the inhibitory effect of α-MSH may be mediated via induction of anti-inflammatory cytokines such as IL-10. On the other hand, the effect of α-MSH on the elicitation phase could be explained by its downregulating capacity of endothelial cell adhesion molecule expression required for adhesion and transmigration of inflammatory cells, as has been shown in vitro (122, 321).

Recent studies indicate that α-MSH may exert its immunosuppressive effects by altering the function of antigen-presenting cells. MC1-R is expressed on blood-derived human dendritic cells and α-MSH downregulates CD40 and CD86 expression in these cells via MC1-R (49). Interestingly, this effect correlated with the state of activation of these cells.

POMC peptides may also regulate antibody synthesis in human B cells since α-MSH and ACTH increase IgE release at low concentrations, which is blocked at high concentrations of these peptides (6). α-MSH also increases the release of histamine and leukotriene C_4 from cutaneous mast cells that are capable of releasing mediators of late phase inflammatory responses such as TNF-α (23).

In murine epidermal LCs and Langerhans cell lines (XS52), VPAC-1 and -2 receptors were detected by RT-PCR (869), supporting a regulatory role also for VIP in epidermal inflammatory responses and probably contact hypersensitivity. Furthermore, LC release factors that influence nerve cell differentiation, such as IL-6, NGF, and basic fibroblast growth factor. LC also express receptors for PACAP, VIP, and gastrin-releasing peptide receptors, suggesting a bidirectional communication pathway between LCs and nerves. Moreover, PACAP inhibits cutaneous immune functions by modulating LC activity. In primary murine LCs and in a cell line (XS106), PACAP was capable of inhibiting contact hypersensitivity reactions in vivo. In vitro, this neuropeptide suppressed the ability of DCs to effectively present antigens to T cells by downregulating IL-1β and upregulating IL-10 (442).

Thus cutaneous nerves may regulate LC function by elaboration of certain neuropeptides, whereas LCs may promote the differentiation of nerves by elaboration of IL-6 and possibly other factors. Although the presence of a SP receptor was also observed in LC by radioligand binding assays, the potential biological function of this receptor is still unknown. For more detailed information about the role of neuropeptides in LC function, we refer to recent excellent reviews (465, 539, 869, 871).

As shown in a mouse model, mast cells and neuropeptides may play an important role in immediate hypersensitivity. During an allergic reaction, mast cells become IgE-dependently activated (type I reaction) (665). Additionally, mast cells can be IgE-independently stimulated by neuropeptides such as SP or VIP. Both peptides mediate an edema after being injected intracutaneously, and SP additionally mediates the recruitment of leukocytes (266), which is partially dependent on mast cell degranulation (952). After peptidergic stimulation, mast cells are capable of releasing not only histamine, but several other inflammatory mediators such as IL-6, TNF-α (23, 277), or proteases such as tryptase (173, 547, 808, 812) that may contribute to neurogenic inflammation. Beside their FcϵRI-mediated activation, murine mast cells can be also activated in a receptor-independent fashion by neuropeptides such as SP or PACAP (730, 731). Because of their large cationic capacity, these peptides penetrate the plasma membrane and activate the signal transduction cascade by direct binding to G proteins (746).

E. Wound Healing

There is increasing evidence that the skin-nervous system may play an important role in mediating normal wound healing. Released neuropeptides may participate in many of the inflammatory processes that are crucial for normal wound healing, such as cell proliferation, cytokine and growth factor production, and neovascularization (854, 968). Several clinical observations indicate that damage to the peripheral nervous system influences wound healing, resulting in chronic wounds within the affected area. Delayed wound healing occurred in animal models after surgical resection of cutaneous nerves (500). In addition, patients with cutaneous sensory defects due to lepromatous leprosy, spinal cord injury, and diabetic neuropathy develop ulcers that fail to heal, in spite of aggressive wound care and wound protection (22). Furthermore, destruction of the ophthalmic branch of the trigeminal nerve results in atrophy, scarring, and ulceration of the cornea.

Experimental observations further suggest that neurogenic stimuli profoundly affect wound repair after injury. First, peptides released from sensory nerve fibers during initial stages evoke vascular responses such as blood flow, vascular permeability, vasomotor activity, or neovascularization. Second, neuropeptides released into the environment of tissue damage affect the regulated inflammatory response within the tissue through immunomodulation of several skin cells and recruited immune cells. Third, neuropeptides influence both proliferation and differentiation of various target cells that are involved in wound healing. Both in rat and pig models, injury induces a reversible sprouting of peptidergic nerve fibers adjacent to the wound that increases in proportion to the severity of the injury (11, 26, 432).

The involvement of certain neuropeptides in experimentally induced wound healing (rats) varies within different tissues and species. For instance, decreased concentrations of SP, somatostatin, and CGRP were observed in wounds in rats (695); elevated levels can be observed in others (26, 695). Xinan et al. (949) showed that the SP content was increased in experimental wounds in rabbits. Moreover, depletion of neuropeptide release affects wound repair because animals pretreated with capsaicin show greater severity of experimentally induced ulcers (505) and delayed wound healing of the cornea. Angiotensin II (ANG II) appears to influence tissue repair via activation of angiotensin I receptor (AT1R) in fibroblasts, leading to collagen remodeling, collagen gel contraction, and upregulation of collagen-binding integrins in vitro. This process is inhibited by the AT1R antagonist losartan and specific tyrosine kinase inhibitors, indicating a role of this pathway in ANG II-mediated tissue remodeling (926). Several neuropeptides affect proliferation in vivo. For instance, surgical resection of cutaneous nerves results in delayed wound healing in animal models (500) and topical application of SP in genetically diabetic mice improved reepithelialization and shortened time to wound closure (601).

An important role in wound healing could be also attributed to a neurotrophic factor, namely, NGF. Several studies (56, 324, 474, 670) could demonstrate that NGF plays an important role in tissue repair. It was shown that NGF induces human skin and lung fibroblast migration but not proliferation. In a mouse model, it could be observed that NGF accelerated the rate of wound healing. These findings have encouraged successful treatment of leg ulcers in humans with topical NGF. Thus NGF may play a role in tissue repair and fibrosis.

CGRP promotes proliferation and migration of human keratinocytes (312, 943, 944) and stimulates proliferation in human dermal endothelial cells (311). VIP, however, exerts both inhibitory as well as stimulatory effects on the proliferation of keratinocytes (942–944). There is also evidence that neuropeptides play an important role in angiogenesis during wound healing and inflammation. SP stimulates DNA synthesis in cultured arterial smooth muscle cells (583) and stimulates endothelial cell differentiation into capillary-like structures (936). CGRP in-

duces both increase in cell number and DNA synthesis in cultured endothelial cells, and SP, CGRP, and VIP have been shown to stimulate angiogenesis in vitro and in vivo (239, 311). Both SP and CGRP exert potent proliferative effects on cultured fibroblasts, indicating that neuropeptides may not only affect vascular and immune responses but also influence proliferation of connective tissue cells.

The interaction between neutrophils and endothelial cells plays an important role in early stages of wound healing. SP, for example, induces cell adhesion of neutrophils to the endothelium as well as their chemotaxis, and stimulation of the NK1R on endothelial cells mediates upregulation of ICAM-1 (656), VCAM-1 (657), and P-selectin (143, 679). Within the first days, monocytes and macrophages also appear at sites of injury. The proliferation of these cells can be modified by CGRP, which inhibits the proliferation of peripheral monocytes and, along with somatostatin, prevents macrophage activation and inhibits hydrogen peroxide production in macrophages. At later stages, T cells are recruited to the wound site. SP is capable of inducing LFA-1 and ICAM-1 upregulation associated with increased transmigration of T cells to the wound site in a mouse model (907). Interestingly, neuropeptides can have a number of effects on the function of T cells. SP has pro-proliferative effects in cultured T cells, whereas VIP and somatostatin significantly decrease DNA synthesis in these cells (623, 624, 795). VIP and SP also have different effects on cytokine production in T cells. Whereas VIP downregulates the production of IL-2 and IL-4 in murine T cells, SP can act as a cosignal to enhance the expression of IL-2 in human T cells (138, 584, 948). PTHrP expression is temporarily upregulated in migratory keratinocytes, myofibroblasts, and infiltrating macrophages of guinea pig skin, although topical application of a PTHrP agonist did not change the healing rate or morphology in these wounds (74, 75).

NEP expression appears to be both increased and redistributed in the wound environment during wound healing, indicating a role for neuropeptide-degrading enzymes in this process (601). In normal skin, NEP immunoreactivity was restricted to the basal layer, whereas during wound healing, NEP was additionally detected in the suprabasal layer of human skin.

Animal studies strongly support a role of neurotrophins during wound healing. To directly compare biological activities of the neurotrophins NT-4 and BDNF in vivo, Fan and co-workers (238) replaced the BDNF coding sequence with the NT-4 sequence in mice (Bdnfnt4-ki). Interestingly, NT-4 supported more sensory neurons than BDNF. In addition, homozygous Bdnfnt4-ki/nt4-ki mice showed reduced skin lesions, suggesting an important role for NT-4 in tissue remodeling and wound healing.

Future studies using transgenic and knockout animals in which certain components of the neurological system are overexpressed or deleted by homologous recombination may make it possible to examine the role of the cutaneous nervous system in normal and delayed wound healing (474).

F. Pruritus

Pruritus can be described as an "unpleasant sensation provoking the desire to scratch" (912). Anatomically it is localized to the skin or mucosa and has a punctuate, phasic quality. Although pruritus is experienced as a sensation arising in the skin, strictly speaking, it is an extracutaneous event, a product of the CNS. The intensity of itch we feel, e.g., after an insect bite, represents a neuronal projection of a centrally formed sensation into defined regions of the integument (localized pruritus), or into large territories of our body surface (generalized pruritus) (621, 914).

Clinically, pruritus is one of the most frequent symptoms of skin diseases and has a high impact on quality of life. It also can be a leading symptom of extracutaneous disease (e.g., malignancy, infection, metabolic disorders) (293). Thus understanding the mechanisms and mediators that lead to effective therapeutic interventions are challenging (71, 621, 791, 805, 954). Because removal of the epidermis abolishes pruritus and the selective block of myelinated nerve fibers does not abolish itch sensation, polymodal C fibers, predominantly mechano-heat-sensitive C fibers, and probably subtypes of Aδ fibers appear to be crucial for mediating chemical, mechanical, probably osmotic, thermal, or electrical stimuli to the spinal cord and CNS, resulting in the symptom of itching. Accordingly, both the PNS and CNS coordinate the sensation of itch, which results in the autonomic reflex of scratching.

A wide range of peripheral itch-inducing stimuli that are generated within or administered to the skin can trigger pruritus. An armada of mediators (Table 1) including amines (histamine, serotonin in rodents), prostanoids (prostaglandins, leukotrienes), kinins, kallikreins, proteases (tryptase), cytokines, protons, and others suffice to produce itching and/or edema and erythema upon stimulation.

The most extensive substance studied so far is histamine, which has a well-established role in mediating pruritogenic effect in urticaria. Recently, additional histamine receptors were cloned and characterized such as histamine-receptor-4 (H4R), for example. H4R is associated with the induction of itch in mice (50). In addition, H3R is involved in scratching behavior of mice (350). When positron emission tomography was used after histamine application, certain areas of the CNS were found to indeed participate in itch perception by humans (353). Furthermore, patients with atopic dermatitis appear to have an altered histamine response and a decreased ability of sensory nerves to signal itching to the CNS (332).

However, the fact that antihistamines fail to eliminate itch in many other skin diseases (e.g., atopic dermatitis) suggests that other mediators and mechanisms are involved in this process. Intradermal injection of neuropeptides such as SP into human skin provoke itch, along with the characteristics of "neurogenic inflammation," such as wheal and flare. These responses were inhibited by antihistamines and compound 48/80, indicating an involvement of mast cell mediators in this process. This is also the case for VIP, somatostatin, secretin, and neurotensin (334, 691, 912, 913). Interestingly, the potent vasodilatator CGRP does not stimulate histamine release from mast cells and does not mediate pruritogenic effects in humans (249). However, there is evidence that SP-induced itch responses can be mediated by NK1R activation in mice (20), supporting a direct effect of SP in mediating pruritus in vivo.

Intracutaneous injection of both VIP and ACh induces wheal, flare, and a dose-dependent pruritus in healthy skin and in patients with atopic dermatitis. However, the subjective pruritus score did not differ between combined injections of VIP and ACh from ACh injections alone (691), suggesting a predominant role of ACh over VIP involved in the pathophysiology of pruritus in patients with atopic dermatitis. Moreover, a higher density of sensory nerve fibers with a larger diameter was observed by electron microscopy in lichenified lesions of atopic dermatitis (886). In notalgia parestethica, a neuropathia characterized by pruritus, pain, and hyperalgesia, immunostaining to several neuropeptides revealed that affected areas had a significant increase in intradermal nerve fibers as well as epidermal dendritic cells, suggesting that sensory nerve fibers are involved in the pathogenesis of this disease. Agents such as capsaicin, which deplete neuropeptides from sensory neurons, have been shown to have a therapeutic effect in diseases associated with pruritus and pain.

Intradermally injected morphine induced an itch response, and low doses of β-endorphin or enkephalins intensify histamine-induced pruritus, although single doses of opioids at the same concentrations did not provoke pruritus (248, 249). Opioid μ-receptors seem to play an important role in the central neural mechanisms of itch sensation, because in addition to analgesia, morphine provokes pruritus when applied intrathecally and the opioid antagonist naloxone is effective in abolishing or diminishing itch in mice, monkeys, and humans (55, 863, 864). Thus endogenous opioids may participate in the transmission or modulation of pruritic stimuli to the cortex, although the precise mechanisms and the central role of opioids for itch responses are still unknown. Opioids may be involved in the pathophysiology of cholestatic pruritus (392, 393). Importantly, effective treatment of pruritus varies within different itchy disorders. For example, in contrast to skin-derived pruritus, cholestatic pruritus can be significantly reduced by application of an antagonist to 5-hydroxytryptamine, although serotonin is synthesized in platelets and probably human melanocytes, not in human mast cells or nerve fibers (385).

Like opioids, cannabinoids have been the focus of pruritus research (437, 621, 805), partly because cannabinoid receptor-1 (CB1) and TRPV1 are highly colocalized in small-diameter primary afferent neurons (437). Moreover, CB1 agonists effectively suppressed histamine-induced pruritus in humans (225), suggesting involvement of CB1 and cannabinoids in mast cell-dependent itching. Furthermore, under inflammatory conditions (763), endogenous cannabinoids such as anandamide are capable of activating and sensitizing TRPV1, thereby switching their neuronal effect from inhibition (9) to excitation and sensitization (890). Finally, cannabinoid receptors are also constitutively expressed by human nonneuronal skin cells such as keratinocytes (501, 790) and induce release of β-endorphin from murine keratinocytes (361). Thus cannabinoids may be involved in the neuronal-nonneuronal cellular network of pruritogenic and painful stimuli arising in or from skin. Consequently, coadministration of a TRPV1 agonist with a CB1 agonist would lead to an antipruritic response and may prevent acute burning sensations induced by capsaicin stimulation, because CB agonists (e.g., anandamide, HU210) would prevent the excitation induced by capsaicin (676, 692).

Actually, the idea that proteinases, e.g., those from plants or bacteria, are involved in the induction of pruritus is rather old (752). Papain and trypsins, as well as tryptase, are capable of inducing itch responses in humans. This may at least in part be mediated by the activation of PARs. Interestingly, PAR_2 was shown to be involved in the pathophysiology of itching in atopic dermatitis patients. Accordingly, the concentration of the ligand, tryptase, was also enhanced, suggesting a role of the tryptase-PAR_2 system in this context. Interestingly, the concentration of histamine was not enhanced in lesional skin of the patients (810). These results were recently confirmed in experimentally induced murine itch models, using either PAR_2 agonists in mice or the trypase inhibitor nafomastate (883).

Very recently, a new itch pathway was identified in atopic dermatitis that linked the inflammatory and pruritic response via the IL-31 pathway, because mice overexpressing IL-31 developed skin lesions and pruritus that were similar to this disease (212). Moreover, the receptor for IL-31, IL-31RA, was found to be highly expressed in a mouse model of atopic dermatitis (781). This finding sheds a new light on the interaction between cytokines and peripheral nerves in pruritus, although the role of this interaction in humans is not yet known.

Unfortunately, because adequate animal models do not exist, most knowledge about the mediators that cause itch derives from studies with humans. These studies may

potentially be artificial, depending on the study protocol. Therefore, future studies with specific agonists and antagonists to neuropeptides and their receptors, endopeptidases, and proteases, as well as the pharmacological modulation of peripheral, spinal, or central neuronal mechanisms will be helpful to determine the role of sensory nerves and develop better treatments for pruritus.

XI. THERAPEUTIC APPROACHES FOR THE TREATMENT OF CUTANEOUS DISEASES WITH A NEUROINFLAMMATORY COMPONENT

Since our understanding of the interactions of the skin and nervous system continues to expand, novel therapies will likely be developed to treat the inflammatory skin diseases that are mediated through neuroinflammation. Specific pharmacological targets for the development of new agents will include the neuropeptides released in the skin, neuropeptide receptors expressed on target cells in the skin, proteases that degrade neuropeptides, agents that modify the function of vanilloid receptors, and growth factors that influence cutaneous innervation. These approaches generate promises of more specific therapies for a wide range of chronic, debilitating skin diseases.

Most clinical experience so far has been developed with the topical agent capsaicin. The usefulness of capsaicin has been demonstrated in several inflammatory diseases, including intestinal and airway inflammation or arthritis. Capsaicin was effective for the treatment of painful diabetic neuropathy (684), cold urticaria (359), atopic dermatitis (929, 930), herpes infection, tumor pain, and different forms of pruritus (491). Thus capsaicin and its analogs appear to be useful to reduce pain, pruritus, or neurogenic inflammation. Capsaicin was effective in some patients with ophtalmicus neuralgia due to herpes zoster (256, 410, 530). Pretreatment of patients with IgE-mediated responses to capsaicin, for example, significantly reduced the flare response after histamine or SP injection but enhanced erythema responses after UV irradiation, tuberculin reaction, and contact dermatitis (918). These contradictory skin reactions are probably due to more complex mechanisms of neuropeptide regulation and distinguished receptor stimulation in various diseases that are not completely understood. These reactions also point out the need for further studies about the role of capsaicin and more specific and potent antagonists to TrpV1 in human skin diseases, especially because the side effects of topical capsaicin treatment (such as burning sensations and hyperesthesia) currently limit its use. Furthermore, capsaicin treatment was ineffective in some patients (256). One alternative may be resiniferatoxin, an ultrapotent analog of capsaicin (reviewed in Ref. 70). Further pharmacological and clinical studies and the development of new capsaicin analogs and synthetic capsaicin receptor ligands are indispensable to clarify the effectiveness of capsaicin as a therapeutic agent for skin diseases (43, 69, 390, 471, 842).

Other currently more experimental treatments for cutaneous neuroinflammation include the use of UV irradiation. UVA irradiation, for instance, modulated the expression of tachykinin receptors in atopic dermatitis (793). Topical treatment with the tricyclic antidepressant doxepin significantly inhibited histamine- or SP-induced weal and/or flare responses in patients with atopic dermatitis (697), suggesting a new therapeutic approach to mast cell- and neuropeptide-associated diseases. A major drawback of this therapy, however, is the sensitizing capacity of this drug leading to allergic contact dermatitis.

Cannabinoids have been shown to reduce hyperalgesia and neurogenic inflammation via interaction with cannabinoid-1 receptors and inhibition of neurosecretion (CGRP) from peripheral terminals of nociceptive primary afferent nerve fibers in rat hindpaw (675, 676). Moreover, cannabinoid-2 (CB-2) receptor inhibition may be beneficial for the treatment of pain and itch (361).

SST and its receptors seem to play a regulatory, largely inhibitory, role in immune responses. A SST analog peptide (SMS 201–995) enhanced the immunosuppressive effect of FK506 in rat spleen cells in vitro. Moreover, combined therapy with the SST analog and FK506 at very low doses led to effective immunosuppression without any undesirable side effects, indicating a therapeutic effect of this peptide analog by decreasing the toxicity of other immunosuppressives (631). This finding is in good agreement with the finding that neuronal sst, after stimulation by capsaicin, exerts anti-inflammatory effects in a murine model of experimentally induced contact dermatitis (41).

Several papers indicate the potential of proteases and PARs as targets for anti-inflammatory therapy (340, 608, 807).

The finding that IL-31 is a cytokine that links the mechanism of inflammation and pruritus in atopic dermatitis opens up a new field for specifically targeting inflammatory mediators that are associated with the neuroimmune network in the skin. Thus antagonists for IL-31R may be beneficial for the treatment of inflammation and pruritus in atopic dermatitis patients.

In summary, in view of a key role of interactions between the nervous and immune systems of the skin through various mediators (Table 2), the possibility of producing anti-inflammatory agents against ligands or receptors will be an important task for research in dermatological therapy.

XII. CONCLUSIONS AND FUTURE DIRECTIONS

There is no doubt that the nervous system of the skin is much more than cutaneous nerve fibers that transmit sensory impulses to the CNS. It is now well appreciated that complex interactions exist linking sensory and autonomic nerves to the immune and endocrine systems. Moreover, the skin itself generates neuromediators and neurotrophic factors that target nerve fibers, thereby modulating inflammation, immune responses during host defense, pain, and pruritus.

When stimulated, nerve fibers release neuromediators of different chemical origin, predominantly peptides, which target skin cells expressing specific neuropeptide receptors. Homeostasis is accomplished by peptidases, which degrade neuropeptides, and neurotrophins that influence innervation and receptor expression in ganglia of primary afferent neurons.

The bidirectional communication between skin cells and the nervous system acts as a homeostatic unit to guarantee regulation during physiological and pathophysiological states. Modern techniques and recent knowledge about molecular mechanisms of neuropeptide and neuropeptide receptor functions have provided exciting insights into a complex network of the nervous and immune system of the skin. However, the precise ability of the cutaneous nervous system to regulate pro- and anti-inflammatory events as well as host defense remains to be determined.

Thus important questions about the physiological and pathophysiological role of nerves in skin function still have to be elucidated. For example, we know that several neuropeptides are released in the skin, but how are they regulated and what is the functional relevance? We also know that several receptors for neuropeptides are expressed in skin tissues, but how are they regulated and what is the impact of these receptors and their potential dysregulation in disease states? What is the significance for the existence of multiple receptor subtypes for one peptide hormone and how are they differentially regulated? Which neuropeptide-degrading enzymes are crucial for skin function and which factors influence the regulation of these enzymes during inflammation or host defense mechanisms? The questions of which ion channels are expressed in the skin and how they are regulated during inflammation, pain, and pruritus also need to be answered before we can ask which proteases are generated during skin pathophysiology and which PAR receptors do they activate? In addition, can antagonists of neuronal PARs suppress neurogenic inflammation, pain, or pruritus? Which receptors for cytokines or chemokines are expressed by sensory and autonomic nerves, and what is their impact in cutaneous neuroimmunology?

Finally, what are the crucial neurological pathways and mediators the skin utilizes to provoke adaptive or maladaptive responses and how can they be influenced leading to healing? The use of morphological, molecular, and pharmacological techniques, along with new genomic and proteomic approaches, will lead to an integrated understanding of the skin as a neuroimmunoendocrine organ during health and disease, and hopefully to new and innovative approaches for the treatment of the many skin diseases that still need to be cured.

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