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Review Article

Neuroendocrine Pathways in Skin Health and Homeostasis: A Systematic Review

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Abstract

The skin is increasingly recognized as a neuroendocrine organ that continuously communicates with the nervous system, linking cutaneous biology with overall wellness. Despite growing interest in the skin-brain axis, there remains limited synthesis of interventional strategies targeting neuropeptides and neurotransmitters to improve skin health. This systematic review aimed to evaluate the current evidence on neuropeptide- and neurotransmitter-based interventions in dermatology, with a focus on mood-related pathways and cutaneous outcomes. A systematic search of PubMed (January 2015-September 2025) was performed, including interventional studies investigating key neuroendocrine mediators in skin disease and regeneration. A total of 68 studies met inclusion criteria, the majority of which were preclinical, with a smaller proportion of randomized controlled trials. Melatonin, substance P modulation and oxytocin demonstrated the most consistent evidence across anti-inflammatory, reparative and psychodermatologic outcomes. Collectively, these findings position neurohormonal signaling as an emerging therapeutic target in dermatology, with potential applications spanning both disease management and aesthetic medicine.

Keywords: Super Bioavailable Itraconazole; Glabrous Dermatophytosis; Body Surface Area

Introduction

The skin, sharing its ectodermal and embryological lineage with the brain, functions as a dynamic neuroendocrine and peptidergic organ capable of producing, releasing and responding to a wide range of neuropeptides and classical neurotransmitters [1,2].

Beyond acting as a physical barrier, the skin maintains a two-way dialogue with the Central Nervous System (CNS), processing stimuli such as pain, pH, temperature and mechanical stress while transmitting signals that influence systemic stress, inflammation and behavior [3-5].

Communication occurs through a cutaneous Hypothalamic-Pituitary-Adrenal (HPA)-like axis and the local production of neuropeptides such as Corticotropin-Releasing Hormone (CRH), β-endorphin, α-Melanocyte-Stimulating Hormone (α-MSH), Calcitonin Gene-Related Peptide (CGRP), Substance P (SP), oxytocin, Vasoactive Intestinal Peptide (VIP) and Neuropeptide Y (NPY), as well as neurotransmitters including serotonin, dopamine and melatonin [6-9]. These mediators regulate pigmentation, wound healing, nociception, pruritus, angiogenesis, inflammation and psychosocial well-being-linking mood, stress and dermatologic health.

Neuropeptides are short peptide messengers packaged in dense-core granules and released to act mainly via G Protein-Coupled Receptors (GPCRs). Neurotransmitters are endogenous chemical messengers stored in synaptic vesicles that transmit signals across synapses and neuromuscular junctions, enabling neurotransmission. Compared with neurotransmitters, the effects of neuropeptides are typically slower in onset and longer in duration, but both systems frequently interact. For example, acetylcholine rapidly triggers skeletal muscle contraction via ionotropic receptors, whereas the neuropeptide substance P drives more sustained itch via GPCRs [10,11]. Both neuropeptides and neurotransmitters may act as transmitters, neuromodulators or neurohormones depending on context and are often co-released-challenging the "one neuron-one transmitter" doctrine [10-12].

In the skin, these signaling molecules are synthesized by keratinocytes, endothelial cells, Langerhans cells, mast cells, melanocytes and nerve fibers and can also be delivered via immune cells [10,13]. By linking the skin-brain axis to local immune, vascular and pigmentary systems, they provide a mechanistic basis for the bidirectional connection between mood and dermatologic disease. Given these wide-ranging roles, modulating cutaneous neuropeptide and neurotransmitter pathways represents a promising therapeutic strategy. This systematic review synthesizes interventional evidence from the last decade on key neuroendocrine molecules relevant to the brain-skin-axis across regenerative processes and common conditions such as psoriasis, vitiligo, rosacea, atopic dermatitis and prurigo.

Methodology

A systematic review was conducted using PubMed to identify all peer-reviewed articles published between January 2015 and September 2025. The protocol was registered with PROSPERO on September 10, 2025 (CRD420241144523). The review focused on mood-related neuropeptides and neurotransmitters synthesized in and active upon, the skin. Molecules of interest included Corticotropin-Releasing Hormone (CRH), Adrenocorticotropic Hormone (ACTH), α-Melanocyte-Stimulating Hormone (α-MSH), β-endorphin, substance P, Calcitonin Gene-Related Peptide (CGRP), oxytocin, serotonin, dopamine and melatonin.

Search results were limited to studies addressing skin conditions relevant to wellness and disease (e.g., aging, psoriasis, vitiligo, acne, rosacea, prurigo). Skin neoplasia and systemic causes of pruritus were excluded, as were their mechanisms and treatments (e.g., chemotherapy) falling outside the scope of this review.

Eligible studies were restricted to English language, interventional investigations, including in vitro, ex vivo and animal studies with clear translational intent, as well as human clinical trials. Review articles, case reports, conference abstracts and articles without available full text were excluded.

Two authors (EK and AMH) independently and blindly screened all records. Discrepancies were resolved by full-text review and discussion until consensus was achieved. Extracted data included intervention, outcomes and level of evidence. Studies were classified according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence, with most corresponding to level 2 evidence or preclinical translational studies.

Results

A total of 68 studies met inclusion criteria and were analyzed for study design, level of evidence, intervention type and outcome direction (Table 1). The selection and screening process are summarized in the PRISMA-style flow diagram (Fig. 1). The majority of studies (n = 53, 77.9%) were Level 5 evidence, consisting primarily of *in-vitro* or *ex-vivo* experimental models. Fourteen studies (20.6%) were Level 2 randomized controlled trials, while one study (1.5%) represented Level 3 evidence. Study designs were most commonly *in-vitro* or *ex- vivo* (n = 43, 63.2%), followed by clinical or human trials (n = 18, 26.5%) and animal or mixed *in-vivo* models (n = 7, 10.3%).

The most frequently studied interventions included melatonin (n = 15), substance P (n = 14) and oxytocin (n = 7). Other commonly investigated agents were serotonin / 5-HT (n = 5), Calcitonin Gene-Related Peptide [CGRP] (n = 4), α-melanocyte-stimulating hormone [α-MSH] (n = 4) and botulinum toxin (n = 3). These interventions spanned a range of dermatologic applications, including inflammation, pigmentation, wound healing, hair cycle regulation, photoaging and stress-related cutaneous responses.

Among clinical and human studies, the median sample size was 35 participants (mean = 53; range = 8-204). The largest randomized trials evaluated serlopitant for psoriatic pruritus (N = 204), intranasal oxytocin and psychosocial interaction effects

on wound healing (N = 160) and melatonin or afamelanotide for atopic dermatitis and vitiligo (N = 28-48). Collectively, these data underscore a growing body of evidence supporting neurohormonal and neuropeptide pathways as modulators of skin health and disease, with the strongest evidence to date favoring melatonin, substance P and oxytocin for their roles in anti-inflammatory, reparative and psychodermatologic outcomes.

Neuropeptide/Neurotransmitter	Pathway	Receptor/Target	Key Mediators Released/Effect	Cutaneous Relevance
Corticotropin-Releasing-Hormone (CRH)	HPA axis; upstream regulator of POMC/melanocortin pathway	CRH-R1, CRH-R2	↑ NF-κB (cell-type dependent); ↑ IL-1, IL-6, TNF-α; activates POMC cascade	Inflammation, sebogenesis, stress responses
Adrenocorticotropic-hormone (ACTH)	HPA axis; POMC / melanocortin pathway	MC1R; adrenal receptors	↑ Cortisol; melanocortin signaling	Stress buffering, immunomodulation, pigmentation
α-Melanocyte-Stimulating Hormone (α-MSH)	POMC / melanocortin pathway (HPA downstream)	MC1R, MC5R	↑ Melanin; ↓ NF-κB; ↓ pro-inflammatory cytokines	Pigmentation, anti-inflammatory effects
β-endorphin	POMC-derived; opioid system	μ-opioid	↓ NF-κB; ↓ mTORC1; ↑ MAPK/ERK signaling	Analgesia, wound healing, angiogenesis
Substance P	Neurogenic inflammation; neuroimmune signaling	NK1R	↑ Mast cell degranulation; ↑ histamine, TNF-α, IL-1; plasma extravasation	Pruritus, inflammation, edema
Calcitonin gene-related peptide (CGRP)	Neurogenic inflammation; neurovascular signaling	CGRP	↑ Vasodilation; ↑ cutaneous blood flow; ↑ IL-6, TNF-α	Flushing, rosacea, neurovascular inflammation
Oxytocin	Psychosocial; anti-inflammatory/antioxidant signaling	OXTR	↓ IL-6; ↓ ROS; ↑ glutathione; ↑ ERK, Nrf2; ↑ T-reg cells	Wound healing, barrier repair, anti-inflammatory, regenerative/rejuvenation effects
Serotonin	Neurotransmitter; immune modulation; melatonin precursor	5-HT	Modulates cytokines; mast cell co-release with histamine; precursor to melatonin	Pruritus, inflammation, pigmentation
Dopamine	Neurotransmitter; oxidative stress/immune modulation	D1, D2	Receptor-dependent effects: D1 → ↑ angiogenesis, proliferation; D2 → ↓ healing; ↑ ROS (quinones, H_2O_2)	Wound healing modulation, immune regulation, vitiligo (oxidative stress)
Melatonin	Circadian; antioxidant/mitochondrial protection	MT1, MT2	↑ Antioxidant enzymes; ↓ ROS; ↓	Photoprotection, anti-aging, pigmentation, hair growth

			tyrosinase; DNA repair	
Acetylcholine (Ach)	Neurotransmitter; cholinergic signaling; neuroimmune modulation	Muscarinic and nicotinic receptors	Regulates keratinocyte proliferation and differentiation; modulates vascular tone and sweat production; indirectly ↓ substance P and CGRP (via BoNT)	Barrier homeostasis, inflammation modulation, sweating, vascular regulation

Table 1: Neuropeptide/Neurotransmitter pathways details.

Discussion

Neuropeptide Mediators of the Skin-Brain Axis

CRH and the Cutaneous HPA-like Axis

The skin contains a localized equivalent of the Hypothalamic-Pituitary-Adrenal (HPA) axis that mirrors its systemic counterpart but functions independently to coordinate local stress responses. Keratinocytes, mast cells and sebocytes release Corticotropin-Releasing Hormone (CRH) in response to Ultraviolet (UV) radiation and inflammatory cytokines [14]. CRH is produced both centrally in the hypothalamus and peripherally in cutaneous cells.15 CRH acts through two receptors: CRH-R1, widely expressed in keratinocytes, melanocytes and fibroblasts within the epidermis and dermis and CRH-R2, expressed predominantly in dermal structures [15,16]. Binding of CRH to its receptors induces NF-κB activation and upregulation of pro-inflammatory mediators such as IL-1, IL-6 and TNF-α [17-19].

Clinical and translational studies illustrate CRH's dual role in skin physiology. In a split-face 28-day trial, a topical phytomimetic CRH-R1 antagonist reduced baseline and heat-induced microcirculation/redness, accelerated recovery following sodium lauryl sulfate irritation and modestly improved wrinkles in adults with stress-reactive skin [20]. Immunohistochemistry studies also implicate CRH in acne pathogenesis, with greater CRH immunoreactivity in sebaceous glands from acne lesions compared with non-lesional or healthy skin [21]. In psoriasis, lesional CRH/CRH-R1 expression has been variably reported as decreased or increased, supporting a stage-dependent or biphasic model in which acute stress drives CRH upregulation, while chronic plaque disease reflects receptor downregulation or exhaustion [22,23]. This mirrors systemic stress biology, where cortisol can be acutely anti-inflammatory yet contribute to chronic inflammation when dysregulated [24]. Through its downstream cleavage of Proopiomelanocortin (POMC), CRH also regulates ACTH, α-MSH and β-endorphin production, positioning it as a central orchestrator of the skin's neuroendocrine stress axis [25,26].

POMC-Derived Peptides

Binding of CRH to CRH1 and CRH2 triggers downstream activation of Proopiomelanocortin (POMC), which then undergoes tissue-specific cleavage by Prohormone Convertases (PC1/3 and PC2) to generate the melanocortins-Adrenocorticotropic Hormone (ACTH), α-Melanocyte-Stimulating Hormone (α-MSH), β-MSH and γ-MSH-as well as β-endorphin and β-lipotropin [2,27]. In the skin, POMC and its derivatives are expressed in keratinocytes and melanocytes [28]. These derivatives bind Melanocortin Receptors (MCRs), of which MC1R and MC5R are most prominent in skin, with roles in pigmentation, barrier function, immune modulation and anti-inflammatory signaling [29-31].

Adrenocorticotropic Hormone (ACTH)

Adrenocorticotropic Hormone (ACTH) regulates systemic glucocorticoid production and also binds melanocortin receptors within the skin to modulate inflammation and maintain homeostasis [25,26]. Through cortisol release, ACTH contributes to stress buffering, repair and regeneration of skin, but chronic activation of the HPA axis with sustained cortisol elevation has been linked to impaired psychological well-being [32]. Conversely, proper functioning of the skin's local HPA axis may mitigate stress responses and support systemic homeostasis [33,34]. Clinically, ACTH analogues have demonstrated efficacy in refractory dermatomyositis, improving both cutaneous and muscular manifestations while reducing steroid dependence [35,36]. Although

ACTH is best recognized for stimulating cortisol release, evidence suggests its steroid-sparing benefit in dermatomyositis is mediated by direct anti-inflammatory and immunomodulatory signaling through melanocortin receptor binding [37].

α-Melanocyte-Stimulating Hormone (α-MSH)

α-Melanocyte-Stimulating Hormone (α-MSH) regulates pigmentation through MC1R activation and also exerts anti-inflammatory effects. Afamelanotide implants have demonstrated clinical benefit by improving photoprotection in erythropoietic protoporphyria and accelerating repigmentation in nonsegmental vitiligo, with particularly strong responses in darker phototypes [38-40]. In melasma, topical α-MSH antagonists reduced pigmentation with fewer adverse effects compared with hydroquinone [41,42]. Conversely, misuse of unregulated synthetic analogues such as "melanotan" has been associated with melanocytic atypia and melanoma [43].

β-Endorphin

β-Endorphin, a POMC-derived endogenous opioid peptide, is synthesized in keratinocytes and melanocytes and released in response to stressors such as Ultraviolet (UV) and blue light exposure [28,44]. By engaging μ-opioid receptors in both the skin and central nervous system, β-endorphin mediates analgesia, reward and stress-buffering effects, contributing to pleasure and restoration of homeostasis. Physiologically, levels normally surge with acute stress or aerobic exertion to elevate pain thresholds and reestablish balance, whereas in chronic stress states such as fibromyalgia, baseline β-endorphin is reduced and the stress- or exercise-induced rise is blunted [44].

Within the skin, β-endorphin contributes to homeostasis, analgesia, tissue integrity and pigment regulation. In keratinocytes, β-endorphin attenuates UVB-induced inflammation through inactivation of NF-κB and blockade of mTORC1 signaling, while also promoting angiogenesis, wound healing and post-procedural recovery, largely via MAPK/ERK signaling cascades [45,46]. Its photobiological activity further links cutaneous production to systemic effects: keratinocyte-derived β-endorphin rises in response to UV and blue light, contributing to circulating levels and associated sensations of well-being [47-49]. These effects align with experimental data demonstrating that UV exposure can drive hedonic and even addictive behaviors, mediated by β-endorphin's reward properties [49,50].

Although often regarded as a "well-being" neuropeptide with roles in tissue repair and photodamage defense, β-endorphin dysregulation appears in pathology [46,50,51]. Elevated plasma β-endorphin and an increased β-endorphin/dynorphin ratio have been observed in patients with asteatotic dermatitis and psoriasis, while its capacity to enhance lipolytic activity in Malassezia may exacerbate seborrheic dermatitis [52,53]. These dual effects underscore β-endorphin's broad influence, spanning protective, regenerative and maladaptive pathways in skin and systemic health.

Neurogenic Inflammation/Vascular Axis

Neurogenic inflammation arises from nerve activation, leading to the release of neuropeptides and rapid plasma extravasation with edema and contributes to pain disorders such as headache and inflammatory skin disorders such as atopic dermatitis, psoriasis and rosacea [54]. In the skin, neuropeptides such as substance P and Calcitonin Gene-Related Peptide (CGRP) are key mediators in neurogenic inflammation. Nociceptors are a subset of primary afferent neurons, with cell bodies located in the dorsal root ganglia and trigeminal ganglia, that respond to tissue injury and are made up of both unmyelinated C-fibers and myelinated Aδ-fibers innervating skin, muscle, joint and visceral organs. TRPV1 (transient receptor potential vanilloid 1) is an ion channel expressed on a subset of cutaneous unmyelinated C-fibers, which mediate slower, diffuse "second pain," as well as lightly myelinated Aδ-fibers, responsible for faster, sharp "first pain". TRPV1 acts as a sensor for noxious endogenous and exogenous stimuli such as temperature, pH changes and capsaicin [55]. Activated TRPV1 produces a direct calcium influx which leads to the release of Substance P (SP) and CGRP [56]. CGRP drives potent vasodilation and increased cutaneous blood flow, while SP promotes plasma extravasation, vasodilation, pruritus and mast cell activation, together contributing to edema and inflammatory responses. Several studies show that TRPV1 is upregulated in inflammatory skin conditions such as rosacea, prurigo and atopic dermatitis [57,58].

Several studies on chronic pruritus disorders have investigated antagonists of the substance P receptor (NK1R), a G protein-coupled receptor. One trial showed significant itch reduction, while others were modest or equivalent to placebo [59-62]. Interestingly, several studies have examined botulinum toxin (BoNT) not for its well-known action of blocking acetylcholine

release at the neuromuscular junction, but rather for its ability to reduce the release of neuropeptides such as substance P and CGRP, to improve skin conditions such as rosacea and psoriasis [63-65].

Psychosocial Axis

Vasopressin

Vasopressin (VP), also known as antidiuretic hormone, is a nonapeptide that shares seven of nine amino acids with oxytocin and as such is closely related and co-expressed with oxytocin in hypothalamic magnocellular neurons. VP is classically recognized for its role in water homeostasis and urine concentration [66,67]. Interestingly, related to this physiology, urine marking is a well-established territorial behavior across species and is strongly tied to vasopressin signaling, aligning with its central role in territoriality and male-predominant aggression [68,69]. Vasopressin, along with oxytocin, has also been shown to play a role in social bonding, physiological stress responses and wound healing [70]. In one human study of 37 couples, small blisters were created on the forearm and during the healing time, endogenous oxytocin and vasopressin levels were measured [70]. Higher vasopressin levels were associated with improved interpersonal communication and accelerated wound repair in women, supporting a complementary role in linking social bonding to cutaneous healing within shared neurohormonal pathways. However, our review did not identify any interventional studies investigating vasopressin specifically for skin wellness and most dermatologic references to vasopressin describe deleterious outcomes when used for refractory shock, including ischemic necrosis, purpura fulminans and impaired cutaneous microcirculation [71].

Oxytocin

Oxytocin, a neuropeptide produced by keratinocytes and fibroblasts, is released in response to sensory stimuli such as C-tactile nerve activation, Adenosine Triphosphate (ATP) signaling, skin-to-skin contact and mechanosensitive ion channel activation [72]. This release occurs both centrally and peripherally, influencing emotional and physiological states. Through its receptor (OXTR), oxytocin modulates pro-inflammatory cytokine release and enhances antioxidant defenses in the skin [29]. For example, knockdown of OXTR was shown to increase reactive oxygen species and decrease glutathione levels in one study, underscoring oxytocin's role in maintaining skin barrier integrity and its relevance to conditions such as atopic dermatitis [73]. Oxytocin also alleviates cellular senescence through the activation of the Extracellular Signal-Regulated Kinase (ERK) and Nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, thereby promoting cellular health [74]. Supporting this, a study demonstrated that enhanced oxytocin levels correlated with lower skin age scores and reduced solar damage through its protective role against inflammatory cytokine release [75]. Beyond its anti-inflammatory effects, oxytocin accelerates wound healing by upregulating T-regulatory cells and mitigating stress-induced delays in the healing process [76,77]. Finally, amplifying oxytocin release through skin-to-skin contact not only enhances skin health but also fosters reduced stress, improved mood and increased feelings of pleasure, as observed during maternal-infant bonding or other forms of affectionate touch [78,79]. Extending this concept, a randomized, double-blind, placebo-controlled study demonstrated that a novel topical formulation designed to modulate epidermal oxytocin and pheromonal signaling pathways improved skin quality, perceived youthfulness, confidence and sexual satisfaction, supporting a link between cutaneous neuroendocrine signaling and psychosocial well-being [80].

Neurotransmitter Mediators of the Skin-Brain Axis

Neurotransmitters, traditionally recognized for their roles in neural communication, are increasingly understood as regulators of skin homeostasis and mood, with local synthesis by keratinocytes, melanocytes and fibroblasts. Beyond signaling in the CNS, they influence pigmentation, immune modulation, barrier function, wound healing and psychodermatology.

Serotonin

Serotonin is an evolutionarily conserved indoleamine monoamine neurotransmitter and immunomodulator, central to the skin-brain axis and a precursor of melatonin. Human skin expresses serotonin, its Synthetic Enzyme, Transporter (SERT) and multiple receptor subtypes, demonstrating that it can produce, release, metabolize and respond to serotonin independently of the brain.81 Functionally, serotonin acts as a paracrine and autocrine signal, influencing keratinocyte and melanocyte proliferation, differentiation, pigmentation and immune activity, while its metabolism to melatonin supports circadian regulation, antioxidant defense and anti-aging processes [2]. Pathologically, serotonin contributes to inflammatory and pruritic disorders. Elevated serotonin has been reported in psoriatic and atopic dermatitis lesions, where it promotes inflammation [81,82]. Released from mast cells with histamine via the IgE-FcεRI pathway, serotonin contributes to histaminergic itch, but it is also a non-histaminergic pruritogen: in atopic dermatitis lesions, serotonin-evoked itch was more intense and not blocked by antihistamines [82,83].

Clinically, serotonergic modulation underlies therapies such as doxepin, mirtazapine, SSRIs and SNRIs for pruritic disorders. In human immune cells such as monocytes, 5-HT2B antagonism dampened cytokine release, supporting its potential in inflammatory dermatoses like AD and ACD [84]. In repair, serotonin stimulated keratinocyte proliferation and migration even in growth factor-deficient medium [85]. In pigmentation, downregulation of 5-HT7 in vitiligo and restoration by agonists supports a role in stress-related depigmentation [86].

Dopamine

Dopamine, a catecholamine neurotransmitter produced by keratinocytes, plays a multifaceted role in skin homeostasis and disease. In the context of vitiligo, locally elevated dopamine appears to be pathogenic: keratinocyte-derived dopamine undergoes oxidation to generate quinones and hydrogen peroxide, which are toxic to melanocytes [87]. Consistent with this mechanism, perilesional vitiligo skin exhibits increased dopamine levels, supporting a model in which excess local dopamine drives oxidative stress and melanocyte loss [88].

Beyond its role in melanocyte toxicity, dopamine exerts tightly regulated, receptor-dependent effects on cutaneous repair. D1 receptor signaling promotes angiogenesis and keratinocyte proliferation, whereas D2 receptor activation suppresses these processes, indicating that the balance of receptor activity determines overall wound-healing outcomes [89]. Dopamine further integrates into cutaneous signaling networks by modulating adrenergic pathways; specifically, it enhances keratinocyte migration through β2-adrenergic receptor blockade [90]. However, these effects are highly cell-type specific: while dopamine can impair wound closure in keratinocytes by reducing migration and matrix metalloproteinase activity, it simultaneously promotes inflammatory mediator release and tissue remodeling in macrophages [91].

Finally, dopamine links cutaneous biology to broader neurobehavioral and environmental processes. In psychodermatology, dopaminergic reward circuitry reinforces the itch-scratch cycle, perpetuating skin damage [92]. Additionally, chronic ultraviolet exposure increases dopamine levels in both the skin and hippocampus, leading to sustained D1/D5 receptor activation and impaired neuroplasticity [93]. Together, these findings position dopamine as a context-dependent regulator of skin pathology, repair and neurocutaneous interactions.

Melatonin

Melatonin is a neuroendocrine hormone synthesized from serotonin in the pineal gland through a light-dependent process. In skin, it functions as an antioxidant and free radical scavenger, with additional roles in anti-inflammation, DNA repair and mitochondrial protection [94]. It also exerts anticancer effects through inhibition of melanoma growth, accelerates wound healing by stimulating keratinocyte proliferation, reduces pigmentation by inhibiting tyrosinase and regulates hair growth via modulation of follicular estrogen response [94].

Neurotoxin-Based Modulation of Skin Inflammation and Barrier Function

Acetylcholine (ACh), traditionally recognized as a parasympathetic neurotransmitter, is also synthesized by keratinocytes and other cutaneous cells, where it regulates keratinocyte proliferation, differentiation, sweat gland activity and vascular tone-functions central to barrier homeostasis and inflammatory signaling [95,96]. Beyond this cholinergic role, BoNT has been investigated for its broader effects on neurogenic inflammation. Rather than acting solely through inhibition of ACh release, intradermal BoNT has been shown to reduce the release of neuropeptides such as substance P and CGRP, with placebo-controlled and pilot studies demonstrating improvements in flushing and erythema in rosacea and benefit in psoriasis [63-65]. Collectively, these findings highlight the multifaceted mechanisms by which BoNT may influence skin physiology, extending its therapeutic relevance from chemodenervation to the management of inflammatory dermatoses.

Distinct from these neuropeptide-mediated anti-inflammatory effects, topical peptide-based neuromodulators have emerged as non-invasive approaches to target acetylcholine-driven neuromuscular signaling. Compounds such as acetyl hexapeptide-8, a SNAP-25-mimetic peptide and dipeptide diaminobutyroyl, a reversible acetylcholine receptor antagonist, act at pre- and post-synaptic levels to reduce neuromuscular transmission, with clinical studies demonstrating improvements in wrinkle severity and potential prolongation of BoNT efficacy [66,67].

Conclusion

This systematic review highlights the skin's role as a neuroendocrine and neurochemical organ, rich in receptors and resident cells that produce and respond to neuropeptides and neurotransmitters governing inflammation, vascular tone, pigmentation, repair and barrier homeostasis. Across diverse experimental and clinical designs, consistent biologic effects were observed in several key pathways, most notably involving melatonin, substance P and oxytocin, which demonstrated the greatest volume of evidence and most consistent therapeutic potential. These findings suggest that neurohormonal and neuropeptide signaling represent integral components of cutaneous physiology and emerging targets for dermatologic intervention. While heterogeneity of models, small sample sizes and limited long-term follow-up remain constraints, recognition of these pathways is shaping a new conceptual and therapeutic frontier-one increasingly framed within the evolving field of "moodceuticals", encompassing interventions that modulate the skin's neurochemical network to enhance health, repair and resilience.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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