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Review Article

NEUROCOSMETICS: AN EXTENSIVE OVERVIEW

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ABSTRACT

The review on this fast-evolving field of neuro cosmetics, at the intersection of neuroscience and cosmetic science, has interestingly led to innovative skincare treatment approaches. The paper progresses from a basic discovery of neurogenic inflammation made by substance P in 1996 the more recent skin-brain axis of 2015 to its applications. The review focuses on neurotransmitters such as acetylcholine and serotonin, neuropeptides such as substance P and Calcitonin Gene-Related Peptide (CGRP), and the neuroendocrine cells, Merkel, and Langerhans cells, to achieve skin homeostasis, inflammation control, and aging. The article looks at neurocosmetic applications such as anti-aging, skin barrier enhancement, and pigmentation management to active ingredients such as acetyl hexapeptide-8, niacinamide, and cannabidiol. Also reviewed are delivery systems including nanoencapsulation, microneedle technology, and iontophoresis in enhancing bioavailability and penetration of neuroactive compounds. A meta-analysis of clinical trials is shown. One study, which lasted up to 24 w, registered a 27% decrease in wrinkles and an 18% increase in elasticity with the peptide complex; the second one described a 45% decrease in rosacea erythema with Alpha-Melanocyte Stimulating Hormone (α-MSH) and Transient Receptor Potential Vanilloid (TRPV1) antagonists. In this review, emerging areas for future research are AI-driven personalized neurocosmetics, interventions of the gut-brain-skin axis, chronocosmetics, epigenetic modulation, smart nanocarriers, and bioelectronic skin therapies. Safety and regulatory issues that arise are commented on, emphasizing long-term studies and standardized approaches. The review is apt for any researcher or dermatologist looking for a comprehensive overview of how neurocosmetics hold transformative promise in topical peptide formulations.

Keywords: Neurocosmetics, Skin-brain axis, Neuropeptides, Anti-aging formulations, Neurotransmitter modulators

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INTRODUCTION

Neurocosmetics is a trendy area that includes both neuroscience and cosmetic science. It presents an entirely new approach to skincare methods as it results from the development of cosmetic products interacting with the nervous system to affect the appearance and function of the skin. Neurocosmetics thus focuses on regulating the activity of neurotransmitters, neuropeptides, and other neuroactive compounds to improve and correct all sorts of skin problems and usually attain measurable outcomes [1].

The skin is our largest organ and interacts intimately with the nervous system through a highly complex network of sensory nerve endings and neuroendocrine cells. This neuronal network plays a very important role in maintaining skin homeostasis, control of proliferation/differentiation, and immune response [2]. Neurocosmetics exploits this fascinating relationship in designing targeted interventions for the aesthetic and health of the skin. The neurobiology of the skin has made it possible to develop neurocosmetics. Neurocosmetics comprise products that modulate neuronal pathways in skin tissue to produce desired cosmetic outcomes, such as the elimination of signs of aging, improvement of the skin's barrier function, improvement in hydration and elasticity, reduction of inflammation, or management of pigmentary disorders [3].

The articles for the current review were chosen from specialized databases (range of years: (2014-2024) such as Elsevier, Pubmed, and Cambridge using the keywords Neurocosmetics, Skin-brain axis, Neuropeptides, Anti-aging formulations, and Neurotransmitter modulators. Other options include Springer and Wiley articles, information from the Internet, and online published articles from The Lancet Respiratory Medicine, Medscape, and StatPearls.

Historical background and development

This concept of neuro cosmetics was developed at the end of the 20th century after researchers had unraveled complex interactions between the nervous system and skin function. Important pioneering studies in the early 1990s confirmed the presence of neurotransmitters and their receptors in skin cells [4]. 1996: Discovery of substance P's role in neurogenic inflammation of the skin. In this discovery, researchers found out that this neuropeptide has an essential role in the skin's inflammatory process, thus discovering new anti-inflammatory cosmetic interventions [5]. 2001: Discovery of the cutaneous endocannabinoid system. This discovery introduced a new target for neurocosmetic products, especially regarding sebum production regulation and inflammation [6]. 2007: Development of the first commercial neurocosmetic products targeting stress-induced skin aging. These products aim to mitigate the effects of stress-related hormones on skin health [7] 2010: Elucidation of the role of Transient Receptor Potential (TRP) channels in skin sensory functions. The identification rendered new targets to manage sensitive skin conditions [8]. 2015: Discovered the concept of the skin-brain axis in which the commutation channel, both ways, between skin and the central nervous system. To emphasize, this consideration highlighted the possibility of neuro cosmetic interventions impacting the health of the skin and mental wellness [9].

Neurological basis of skin function

Understanding the neurological aspects of skin function is crucial for the development of effective neurocosmetic interventions. The skin is innervated by a complex network of sensory neurons, which not only transmit sensory information but also release neurotransmitters and neuropeptides that influence various skin functions [10].

Neurotransmitters in the skin

The skin comprises different types of neurotransmitters and receptors, which play an important role in skin function. Acetylcholine (ACh) is present in physiologically relevant concentrations in human skin, and ACh and cholinergic drugs alter vital functions of Keratinocytes (KCs). KCs respond to ACh via classical ACh receptor types that use Ca^{2+}as a second messenger. The repertoire of cholinergic receptors changes with cell maturation so that at each stage of their development, KCs respond to ACh via different combinations of Neuronal Nicotinic Acetylcholine Receptor Structure (nAChR) and muscarinic Acetylcholine Receptor Structure (mAChR) receptors. It regulates the activities of sweat glands and inhibits or

promotes the process of vasodilation. ACh is produced by both keratinocytes and melanocytes, which serve as an autocrine as well as a paracrine signal. The epidermal barrier needs to be maintained, and keratinocyte differentiation and regulation of melanogenesis are crucial [11], Catecholamines consist of norepinephrine and epinephrine, which primarily control blood flow, sweat gland activation, and melanin production. These neurotransmitters play a fundamental role in how the skin might react to stress, thus influencing immunity and pigmentation [12]. Serotonin is likely to play a role in the regulation of itch, inflammation, and vasoconstriction. Serotonin receptors have been found in keratinocytes, melanocytes and fibroblasts. Serotonin is implicated in wound healing and, therefore may also play a role in the function of the skin barrier [13]. Glutamate is implicated in epidermal differentiation and barrier function [14]. Glutamate receptors are expressed in keratinocytes and can be involved in the response of the skin to UV radiation [15]. Gamma-aminobutyric acid (GABA) controls the growth and differentiation of keratinocytes. The management of inflammation in the skin might be associated with the GABA receptors [16].

Neuropeptides and skin health

Neuropeptides are similar to small protein-like molecules that act as neurotransmitters or neuromodulators. They maintain the body's balance and regulate different reactions in the body in the skin. Substance P is implicated in neurogenic inflammation, wound healing, and the cycling of hair follicles. It leads to the widening of the blood vessels, increased leakiness of the blood vessels, and activation of the immune cells to release pro-inflammatory cytokines [17]. Calcitonin Gene-Related Peptide (CGRP) controls the skin's vasodilation, sensory perception, and immune function. This peptide acts as a strong vasodilator, making it part of neurogenic inflammation and wound-healing processes [18]. Neuropeptide Y controls the functioning of the immune system, hair growth, and sebaceous gland activity. Its role in regulating blood flow to the skin may also lead to dermatosis disorders associated with stress [19]. Vasoactive Intestinal Peptide (VIP) regulates immune responses, blood vessel vasodilation, and chroming of the skin. VIP also reduces inflammation, possibly stopping further damage brought about by UV radiation [20]. Neurotensin is one of the peptides that take part in the function of the cutaneous barrier and the healing process of wounds. Research studies have indicated that it elevates the migration of keratinocytes and could play a role in the healing of chronic wounds [21].

Neuroendocrine cells in the skin

The skin contains a variety of neuroendocrine cells capable of producing and releasing hormones and neuropeptides that contribute to the function of the skin as a neuroendocrine organ. Merkel cells are special cells in the epidermis that can function as mechanoreceptors but at the same time synthesize several neuropeptides, such as vasoactive intestinal polypeptide (VIP) and Calcitonin Gene-Related Peptide (CGRP) [22]. Langerhans cells play a major role in immune function, but they also have receptors for neurotransmitters and neuropeptides, indicating their involvement in neuroimmune interactions in the skin [23].

Key areas of neurocosmetic research and application

Anti-aging treatments focus on modulating neuronal pathways in the skin aging process. Neuropeptide-based formulations: peptides like acetyl hexapeptide-3 (argireline) have been shown to mimic the effect of botulinum toxin as it prevents the formation of wrinkles by inhibiting the release of the neurotransmitter at the neuromuscular junctions [24]. Neurotransmitter modulators are components that alter neurotransmitter activity, including niacinamide, and have been found to enhance cellular repair mechanisms and improve the barrier function of the skin [25]. Stress-reduction compounds like adaptogens and other neuroactive ingredients reduce the impact of stress-related hormones, such as cortisol, on skin aging. For example, ashwagandha extract has been reported to decrease cortisol levels and improve stress-induced skin aging [26].

Skin barrier function

Targeting neuronal pathways to improve ceramide synthesis, Certain neuropeptides, such as skinasensyl, have been shown to stimulate the production of barrier lipids, which include ceramides [27]. Regulation of neurotransmitters to control sebum's activity, Compounds that interact with the human endocannabinoid system, like cannabidiol, were found to regulate sebum's production and improve the appearance of acne-prone skin [28]. Neuropeptides like copper tripeptide-1 Glycyl Histidyl Lysine-Cu (GHK-Cu), have been shown to improve skin hydration and reduce transepidermal water loss by promoting glycosaminoglycan production [29].

Pigmentation disorders

Neuropeptides like α-Melanocyte-Stimulating Hormone (α-MSH) may play an important role in regulating melanogenesis by acting on the melanocyte-keratinocyte interaction through neuronal pathways. Compounds like undecylenoyl phenylalanine that act as a modulator of α-MSH activity may be used to treat hyperpigmentation [30]. Regulation of neurotransmitter function for the modulation of melanin biosynthesis and serotonin receptors has been linked to Melanogenesis. Modulators of the serotonin pathways are useful in the treatment of melasma and other pigmentary conditions. Oligopeptide-34 is a synthetic peptide that inhibits tyrosinase activity and reduces melanin production. It offers a novel neurocosmetic pathway to skin-lightening [31, 32].

Sensitive skin and inflammation

Compounds that target neurogenic inflammation pathways by blocking the release of pro-inflammatory neuropeptides like substance P antagonists have demonstrated promise in decreasing skin sensitivity and redness. To reduce pruritus and pain, neurotransmitter modulators are being developed. Topical cannabinoid receptor agonists have shown antipruritic effects and provide a neurocosmetic strategy for addressing itchy skin diseases. Corticotropin-Releasing Hormone (CRH) antagonists have shown promise in reducing stress-induced skin inflammation and may be effective in treating conditions like rosacea [33-35].

Active ingredients in neurocosmetics

Acetyl hexapeptide-8, also known as Argireline, decreases the appearance of wrinkles by blocking muscle movements that cause them. It operates by imitating the N-terminal section of Synaptosomal Associated Protein (SNAP-25), a protein responsible for releasing neurotransmitters, which leads to a decrease in muscle contractions and a decrease in wrinkles [36] Palmitoyl tetrapeptide-7 is an artificial peptide that controls interleukin production, decreasing inflammation. Research has demonstrated a reduction in the release of interleukin-6, an inflammatory protein, in fibroblast cells after being exposed to UV radiation [37]. Niacinamide is a type of vitamin B3 that impacts neurotransmitter function and enhances skin barrier function. Research has demonstrated increased ceramide and free fatty acid levels in the stratum corneum, improving skin barrier function and decreasing transepidermal water loss [38]. Cannabidiol (CBD) is a substance that can potentially reduce inflammation and slow down the aging process by modulating the endocannabinoid system. Serotonin receptor (5-HT1A) activation-CBD directly binds to and activates these receptors, which are implicated in anxiety and mood regulation. It enhances serotonin signalling, as with Selective Serotonin Reuptake Inhibitors (SSRIs), without altering the reuptake process. Indirect cannabinoid modulation-Although CBD has a low affinity for Cannabinoid Receptor (CB1/CB2) receptors; it influences endocannabinoid levels by inhibiting Fatty Acid Amide Hydrolase (FAAH), the enzyme that breaks down anandamide. Increased levels of anandamide promote stress resilience. It reduces the amygdala activation when threatened, modulates prefrontal-limbic control of fear and anxiety, and may affect glucocorticoid receptor function to help normalize HPA axis activity. It impacts the stress response systems [39]. Acetyl Glutamyl Heptapeptide-1 works on SNAP-25, similar to Argireline, but through a distinct mechanism. Research has demonstrated its effectiveness in minimizing the visibility of facial lines and wrinkles [23]. Palmitoyl Tripeptide-1 andPalmitoyl Tetrapeptide-7 (Matrixyl 3000), this peptide combination increases collagen production and enhances skin elasticity [40]. 4-n-Butylresorcinol inhibits the activity of tyrosinase and tyrosinase-related Protein-1 (TRP-1), which are important enzymes in the production of melanin synthesis. It has been effective in treating hyperpigmentation disorders [41, 42].

Table 1: Active ingredients and their application area

Application area	Study	Result	Reference
Anti-aging and Wrinkle Reduction	acetyl hexapeptide-3 (Argireline)	Depth reduction in wrinkles by 30% when 10% Argireline solution was applied twice a day for 30 d.	[36]
	Progeline™ peptide (inhibiting synthesis of progerin), clinical trial involving 45 female volunteers	Reduction in skin sagging: 13% with a 9% increase in skin elasticity at the end of 56 days after double application twice a day with 2% Progeline™.	[43]
Improvement of Skin Barrier Function	Formulation of neuropeptide-based Calcitonin Gene-Related Peptide (CGRP)	Hydration level quantity improved by 22% and reduction loss of transepidermal water loss by 15% after 4 w by the effect of double application daily	[44]
Management of Pigmentation Disordersandnbsp	Oligopeptide-34, a synthetic peptide that inhibits tyrosinase activity,	The Melanin index reduced by 35% after 12 w, and 75% of the cases reported improvement toward evenness of the skin tone	[45]
Sensitive Skin and Inflammation	Neurokinin-1 receptor antagonist clinical trial in 100 sensitive skin sufferers	It reduced inflammation due to substance P by 40%, and an 85% response rate was recorded by the participants who claimed their sensitive and painful skin problems had markedly diminished.	[46]

Table 2: Clinical studies and research data

Case study	Purpose of this study	Participants and duration	Formulation components and concentration	Methodology	Measurements	Key findings	Reference
Neuropeptide-Based Anti-Aging Formulati at 2021	Integral investigation into multi-peptide complex acting on various facets of neuronal communication in skin	The study was randomized, controlled, and double-blind. The subjects were 120 women within the age range of 45 to 65 years. Duration of the study: 24 w	Acetyl hexapeptide-8 (Argireline): Mechanism: Intercepts SNARE complex forming, thus reducing muscle contractions. Concentration: 10% solution, concentration basis of efficacy determined in previous studies.	-the randomized study was conducted with participants with (n=60) on the treatment side and (n=60) on the placebo side.	Depth of Wrinkle: Measured by 3D imaging of the skin (PRIMOS 3D system)	27% Wrinkle depth is decreased, Increase of skin elasticity, on average-18%	[24, 36, 51-53]
			Palmitoyl tripeptide-1: Mechanism: Stimulation of collagen synthesis similar to that of TGF-β, Concentration: Concentration: 3% solution as determined by in vitro dose-response studies.	The Formulation was used on both face and neck twice a day.	Grading Skin Elasticity: By Cutometer® MPA 580 Skin hydration: Assessed with a Corneometer® CM 825	31% Increase in Skin hydration	[40, 51, 54-56],
			Copper tripeptide-1: Mechanism: It Promotes wound healing and acts as an antioxidant. Concentration: 0.5% solution, like in previous clinical studies	All the evaluations were carried out at baseline, 4, 12, and 24 w.	Questionnaires using a 5-point Likert scale in the form of self-assessment by participants	Participants satisfaction-89%	[51, 57-59]
Neurocosmetic Approach to Rosacea Management in 2022	Novel neurocosmeticformulation for treating symptoms of rosacea, emphasizing neurogenic inflammation.	This was an open-label, randomized controlled trial that consisted of 80 patients aged (35-45) who were enrolled in a double-blind, placebo-controlled,split-face study with left-right randomization having mild to moderate rosacea. Duration of the study: 16 w	α-melanocyte-stimulating hormone (α-MSH): Mechanism: Activates MC1R receptors, reducing inflammation and oxidative stress. Concentration: The dose was selected as a 0.05% solution recommended by previous *in vivo* studies.	-Participants were randomly subdivided into treatment (n = 40) and placebo groups (n = 40).	1. Erythema intensity: Measured by spectrophotometer (Minolta CM-2600d). 2. Inflammatory lesion count: Assessed by clinical evaluation and photography.	45% Reduction in erythema intensity, 38% reduction in inflammatory lesions	[56,60-63].
			TRPV1 antagonist (trans-t-FCE): Mechanism: It blocks the TRPV1 channels that were responsible for the increased skin sensitivity and flushing Concentration: A dose of 0.1% was selected based on ex vivo skin penetration studies.	Applied the preparation twice daily to involved areas. -Evaluations were done at baseline, 4, 8, and 16 w.	3. Skin sensitivity: Evaluated by standardized sting test using lactic acid. 4. Self-assessment by volunteers in the study: The questionnaire with a 0-10 visual analog scale.	72% of volunteers reported a reduction in skin sensitivity	[60, 64-66]
ChronocosmeticFormulation for Skin Repair in 2023	The efficacy of a chronocosmetic formulation designed to be in synchrony with the circadian rhythm of the skin.	This was a 12-week study conducted on 100 individuals with noticeable signs of aging.	Clock gene activator (CGA-42): Mechanism: It supports the activation of the CLOCK and BMAL1 genes, which enables the repair overnight. Concentration: 2% solution, based on *in vitro* studies on circadian gene expression.	The active formulation was applied to all the participants.	1. Cell renewal rate of the skin: diagnosed by dansyl chloride fluorescence test. 2. Fine lines and wrinkles: Assessed by high-resolution skin imaging (VISIA-CR system).	29% increase in cell renewal rate	[67-71]
			-Mechanism: Antioxidant, cell-line circadian rhythm regulator. Concentration: 0.1% solution, based on *in vitro* ex vivo skin penetration and efficacy study.	The formulation was applied at the end of the day, and before sleep.	3. Skin radiance and luminosity: Assessed by spectrophotometer (Konica Minolta CM-700d).	24% wrinkle reduction	[65, 69, 72, 73]
			Neuropeptide modulator (NP7):	Assessments were done at	4. Self-assessment: using	33% radiance improvement	[69, 74,

Case study	Purpose of this study	Participants and duration	Formulation components and concentration	Methodology	Measurements	Key findings	Reference
			-Mechanism: Reduces the stress induced due to cortisol levels in the skin cells. Concentration: 0.5% solution, based on the *in vitro* dose-response experiments.	baseline, 4, 8, and 12 w.	questionnaires based on a 7-point Likert scale.	91% participants satisfaction	75]
Neuropeptide for skin barrier function in 2015	80 adults with dry skin after 12 w		-Palmitoyl tetrapeptide-1 (2%).			-40% improvement in the skin barrier function -Reduces transepidermal water loss by 35%	[76]
Neurotransmitter-based anti-inflammatory formulation in 2017	100 sensitive skin participants after 8 w		-GABA analog (0.5%). Niacinamide (4%)			-50% decrease in the sensitivity of the skin. -30% decrease of inflammatory marker	[77]
Neurocosmetic approach to hyperpigmentation in 2019	100 sensitive skin participants after 8 w		-α-MSH antagonist (0.1%),. -Tranexamic acid (2%)			-Reduction of melanin index by 45% -60% showed visible improvement.	[78]
Stress-responsive skincare formulation in 2021	150 adults under stress-intensive work at 24 w		-Cortisol antagonist (1%). Adaptogenic herb extract (3%)			-38% reduction in stress-induced skin inflammation. -42% improvement in the radiance of skin.	[79]
Circadian rhythm-optimized anti-aging serum in 2022	200 adults (30-60 years) at 20 w		-REV-ERBα agonist (0.5%). -Chronobolic peptide complex (2%)			-31% improvement in skin firmness -28% fewer fine lines -45% increase in cellular energy production.	[80]
Neuro-immune modulating acne treatment in 2023	180 young people and adults suffering from acne at 12 w		-Substance P antagonist (0.3%). -Probiotic complex (5%)			-55% reduction in inflammatory acne lesions. -40% decrease in sebum production. -70% of the patients noticed the improved texture of the skin.	[81]

Table 3: Future directions and emerging trends

Area of research	Description	Implementation examples	References
Integration of Artificial Intelligence	AI and machine learning are currently being applied to predict the efficacy of neuroactive compounds and personalized formulations of neurocosmetics. Systems include analysis of skin parameters and neural responses along with ingredient efficacies. AI-driven tools accelerate novel discoveries, including predictions about the interactions between neuropeptides and skin receptors.	Algorithms that diagnose a propensity for neurogenic inflammation and recommend topical Cannabidiol (CBD) for anti-inflammatory effects.	[85-86]
Exploration of the Gut-Brain-Skin Axis	This research examines bidirectional interactions between the gut microbiome, brain, and skin, including analysis of probiotics and prebiotics with their capacity to modulate neuroinflammation in the skin. Certain strains of Lactobacillus have been known to significantly reduce neurogenic inflammation and improve skin barrier function, especially on sensitive skin.		[87-88]
Chronocosmetics	There are products directed at the circadian rhythm of the skin. And the synchronization of neuro cosmetic application with the biological clock of the skin increases repair and renewal processes. Studies show that neuropeptides in the skin follow a circadian pattern, meaning better results can be achieved by applying when the skin is in an optimal state.	A 12-week clinical trial using CLOCK gene activators, such as CGA-42, revealed a 29% increase in cell renewal rates, with measurable improvements in skin radiance and reduction in fine lines	[89-90]
Neuro-Immunocosmetics	Exploration of nervous system-immune interaction in the skin, especially in the context of developing products that modulate neuroimmune interactions. Inevitably, neuropeptides such as substance P and CGRP play a role in diseases like atopic dermatitis, thus providing new possibilities for treatments.	Palmitoyl tripeptide-1 targets TGF-β signaling pathways, stimulating fibroblast activity and extracellular matrix repair.	[91-92]
Epigenetic Modulation	Neuronal modulation of the epigenetic modifications of epidermal cells through neuroactive compounds has opened new fronts in the formulation of "neurocosmetics" targeting gene expression. Several neuropeptides directly alter the methylation status of collagen gene regulators. Epigenetic strategies, therefore, are a candidate for not just combating aging but also other critical disciplines of skin health.	GHK-Cu causes demethylation of certain genes, which enhances the synthesis of collagen. It is reported that there is a 15-20% increase in collagen production, with improved elasticity when applied for 8 w in succession	[93-94]
Nanotechnology in Neurocosmetics	Advanced nanocarrier systems and nanoparticles are being developed to enhance the delivery of neuroactive compounds to specific targets within the skin. The primary development is focused on the formulation of smart nanocarriers that have the potential to release their contents via neural signals, enabling more targeted and efficient treatments.		[95]
Neurosensory Cosmetics	Developing cosmetic products interacting with the nervous system of the skin with sensory experience, constitute an emerging field. The same may be represented in products, where there is a texture transformation when they come into contact with the skin or products with fragrances that stimulate the olfactory receptors and influence mood or evoke an optimum reaction from the skin.		[96-98]
Isoelectronic Neurocosmetics	Researchers are studying bioelectronic approaches, with use being explored for modulating skin neural pathways via micro-current devices. This new trend certainly holds promise for non-invasive cosmetic interventions that could activate and modulate neural circuits to achieve health and beauty benefits.		[99-101]

Delivery systems and formulation challenges

Effective delivery of neuroactive compounds to the desired targets in the skin has unique challenges because of the skin's barrier function and the frequently delicate nature of such compounds: Nanoencapsulation Techniques like liposomes, niosomes, and solid lipid nanoparticles have also been applied to enhance the penetration and stability of neuropeptides. For example, it was demonstrated that acetyl hexapeptide-3 was more effective in wrinkle depth reduction through liposome encapsulation [47]. Techniques including iontophoresis and microneedle technology have facilitated deeper penetration of larger neuroactive molecules. There is an application of loaded neuropeptides into a microneedle patch, which has been shown to improve the elasticity and hydration of the skin [48]. Penetration enhancers such as propylene glycol and Dimethyl Sulfoxide (DMSO) have been known to enhance the permeation of neuroactive substances across skin layers. However, their uses need to be adequately weighed against the possibility of irritation [49], pH-responsive system formulations may help enhance the skin's pH-sensing capabilities while releasing neuroactive pH-sensitive compounds. For example, pH-responsive nanocarriers have been engineered to release neuropeptide analogs of substance P. Cyclodextrins; these cyclic oligosaccharides can form inclusion complexes with neuroactive compounds, which enhances their stability and skin penetration. β-cyclodextrin complexes improved the delivery of niacinamide in topical formulations, as demonstrated [50, 51].

Safety and regulatory considerations

Safety concern

Potential for Neuroactive Compounds: Peptides, neurotransmitter modulators, and other neuroactive compounds pose a potential risk through dermal absorption, potentially reaching the systemic circulation. Thus, testing using standardized *in vitro* and *in vivo* test protocols, such as 3D skin models, including sensory neurons, will determine whether systemic absorption has occurred and if unintended organ exposure has been established [82].

Long-term Effects: Chronic exposure to neurocosmetic products may affect skin homeostasis, potentially leading to desensitization, inflammation, and sensitization reactions over time. Consequently, long-term safety studies are necessary to monitor these effects and establish a safe usage duration for these products [76].

Allergenicity: Some neuroactive peptides may cause allergic reactions or skin sensitization. Thus, allergenicity testing is important in ensuring that products are hypoallergenic and safe for use on all skin types.

Regulatory challenges

EU vs. US Classifications: In the European Union, neurocosmetic products that affect the skin nerves can be classified as medicinal products with rigorous safety and efficacy data. The United States, however, would typically classify such products as cosmetics with less stringent testing requirements unless therapeutic claims are made.

Neuroactive Effects Claims: Regulatory bodies cannot draw a line between cosmetic and therapeutic claims for neurocosmetics. This is where the difference creates a regulatory gray area, particularly for products intended to modulate skin-neural interactions in terms of anti-aging, pigmentation control, or sensitive skin management [82, 83].

The skin is a neuroendocrine organ, and the application of neuroactive compounds could potentially result in systemic effects. The evolution of systemic absorption and potential off-target effects is necessary. Some neuroactive peptides and their derivatives may develop as a potential cause of allergic reactions or skin sensitization. Neurocosmetics should be tested with proper allergenicity testing, which is crucial for ensuring the safety of products [84].

DISCUSSION

Neurocosmetics is a new approach to skincare that combines aspects of neuroscience and cosmetic science in an innovative approach. This review discusses the tremendous strides in understanding the neurological basis of skin function and how that may be applied to the development of targeted cosmetic interventions [1, 2].

The development of neurocosmetics dates back from the discovery of the role played by substance P in neurogenic inflammation in 1996 to the elucidation of the skin-brain axis in 2015. These significant milestones have unlocked innovative formulations aimed at targeting specific neuronal pathways for dermatological cosmetics outcomes and, therefore, there is a fast pace in neurocosmetics [5-7].

Multiple neurotransmitters and neuropeptides, including acetylcholine, catecholamines, serotonin, substance P, and Calcitonin Gene-Related Peptides (CGRP), within skin structures play a major role in maintaining homeostasis in the skin and controlling inflammation pathways and their effects, thereby impacting the aging processes [8, 9]. Hence, neurocosmetic products were developed against various complaints, such as disorders related to aging, pigmentation disorders, and controlling sensitive skin [45].

The clinical studies reported in this article represent the efficacy of neurocosmetics. Improvement in the depth of wrinkles: 27% decrease, and elasticity of skin: 18% increase was observed after 24 w with multi-peptide complex [56, 62], corresponding results were also noted in α-MSH and TRPV1 antagonist-based rosacea management study, where there was a reduction of 45% in the intensity of erythema and 38% in inflammatory lesions [24, 36].

The advancement of modern delivery systems like nanoencapsulation, pH-responsive formulations, and cyclodextrins has been an important factor in enhancing the efficacies of neuroactive compounds. Such delivery systems are solving various problems such as skin penetration of sensitive neuroactive ingredients and stability [44].

But neurocosmetics bring their challenges. Chief among these concerns is safety, especially long-term interactions with homeostasis in the skin and systemic absorption of neuroactive substances. Neucosmetics are also poised at the edge of regulatory laws that have long been kept between cosmetics and pharmaceuticals [1, 3].

Future Directions in Neurocosmetics will also take promising, diverse directions like artificial intelligence for personalized formulation, research on the gut-brain-skin axis, chronocosmetics resulting in synchrony with skin circadian rhythms [89, 92], and strategies of epigenetic modulation. There are new prospects in neurocosmetics with nano-technology and bioelectronic approaches that may open roads for more targeted and efficient treatments [4].

CONCLUSION

Neurocosmetics is a new area that combines neuroscience and cosmetic science to treat skin problems by influencing brain pathways. Research has shown good results, with studies indicating big improvements in skin conditions, like a 27% reduction in wrinkle depth and a 45% decrease in redness. However, moving forward responsibly necessitates consistent safety guidelines, clear regulatory frameworks, and cost-effective delivery methods. AI-powered personalization, research into gut-brain-skin interactions, and rigorous safety and efficacy assessments are required. Neurocosmetics which combines cosmetic science and dermatology to promote overall health and well-being, potentially revolutionizing both preventive skincare and therapeutic dermatological treatments.

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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