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Mini Review

Biomimetic Peptides in Dermatology Interfering with Neurotransmission

Giovanni Greco, Ritamaria Di Lorenzo* and Sonia Laneri

Department of Pharmacy, University of Napoli Federico II, Naples, Italy

***Corresponding author:** Ritamaria Di Lorenzo, Department of Pharmacy, University of Napoli Federico II, Naples, Italy

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Abstract

The process of skin aging involves intrinsic and extrinsic mechanisms that lead to biochemical and structural modifications in the epidermis, dermis, fat tissue and underlying muscles. A variety of natural compounds is currently marketed as active ingredients of topical formulations aimed to contrast or minimize the signs of aging skin. This review summarizes the clinical studies on biomimetic peptides used in dermatology as topical skin anti-aging agents thanks to their ability to interfere with neurotransmission.

Keywords: Biomimetic Peptides; Dermatology; Skin; Anti-Aging; Neurotransmitter Inhibitors; Cosmeceuticals

Transparency

Declaration of financial/other relationships

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Authors contribution

All authors were involved in literature research, screening and eligibility evaluation as well as drafting the article or revising it critically for important intellectual content, and all authors read and approved the final manuscript to be published. R.D.L. takes responsibility for the integrity of the work as a whole, from inception to the finished article and affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Introduction

Skin aging is a complex biological phenomenon deriving from the combination of both intrinsic and extrinsic factors. Specifically, intrinsic aging is a complex and inevitable process depending on several processes, such as cellular metabolism, oxidative stress, hormonal cycle, genetics, and physiological timing. Extrinsic aging is mainly related to repetitive and prolonged skin exposure to dangerous factors, such as environmental pollution, cigarette smoking, alcohol consumption, use of harsh cosmetics, and principally sunlight irradiation (photo-aging) [1]. Skin damage is associated with chronically sustained levels of free radicals [2]. These latter, in turn, trigger inflammatory responses which affect the metabolism of collagen and elastin, thus leading skin to

lose flexibility and strength as well as to gain roughness, dryness, irregular pigmentation, and deep wrinkling [3].

Biomimetic peptides are synthetic analogues of naturally occurring peptides retaining their basic pharmacological activity while offering, generally, at least one of the following advantages over their natural counterparts: smaller molecular weight, greater ease of synthesis, better pharmacokinetic profile (i.e., improved absorption, higher metabolic stability, slower elimination), increased affinity to the pharmacological target, lower toxicity. This review summarizes studies on biomimetic peptides which have been found effective as topical skin anti-aging agents. Among the huge variety of biomimetic peptides, we will focus on those mimicking natural peptides which interfere with neurotransmission.

General characteristics of biomimetic peptides in dermatology

Biomimetic peptides suitable for topical applications are usually obtained as truncated and/or modified original peptides. They are characterized by a suitable lipophilic/hydrophilic balance to penetrate the skin, reach the dermis layer, and interact with their molecular targets. For this purpose, a relatively hydrophilic peptide can be conjugated to the N-terminus with a long-chain fatty acid, thus achieving optimal lipophilicity [4]. It is generally accepted that ideal topic drugs should possess precise chemical and physical properties, specifically a low molecular weight, a logP value measured in the n-octanol/water system between 1 and 3, and a water solubility not less than 1 mg/mL [5]. Therefore, biomimetic peptides used in dermatology are designed or selected by considering the above requirements.

Peptides used as skin anti-aging agents

Most of the peptides applied topically on the face to contrast or prevent skin aging fall into four categories: signal peptides, carrier peptides, enzyme inhibitor peptides, and neurotransmitter inhibitor peptides. Signal peptides, like carnosine and its derivatives [6], trigger a signal cascade leading to an increased expression of collagen, elastin, proteoglycan, glycosaminoglycan, and fibronectin, which represent key components of the extracellular matrix. Carrier peptides chelate copper or manganese ions, thus facilitating their transport into skin cells where they are necessary for the proper functioning of metalloenzymes. Copper chelation also inhibits melanogenesis. Examples of such peptides are well represented by copper tripeptide (Cu2+-GHK) [7] and manganese tripeptide-1 (GHK-Mn2+) [8]. Enzyme inhibitor peptides interfere with the activity of enzymes degrading the protein components of the extracellular matrix. Some soy peptides belonging to the family of such peptides have been reported to counteract skin aging by stimulating the synthesis of glycosaminoglycans and collagen [9]. Neurotransmitter inhibitor peptides interfere with neuromodulators controlling the tone of the facial muscles. This latter family of peptides is the primary object of this minireview and will be discussed in more detail.

Biomimetic peptides acting as neurotransmitter inhibitors

Among the many biomimetic peptides used in anti-aging cosmeceutical products, neurotransmitter inhibitor peptides occupy a prominent place. Once entered the skin, they soften wrinkles and fine lines thanks to their ability to reduce involuntary repetitive contraction of facial muscles [10]. The exact mechanism of action of these peptides can be understood by first recalling the pathway of cholinergic transmission [11]. Briefly, the release of acetylcholine (Ach) from neurons is triggered by a cascade of protein-protein interactions leading to muscle contraction through the involvement of the synaptosomal-associated protein 25 (SNAP-25) which participates to the process of vesicles docking and fusion. SNAP-25 is a constituent of the so-called SNARE complex, which comprises also the vesicle-associated membrane protein (VAMP) and the membrane-associated protein syntaxin. The fusion of vesicles results in the release of Ach into the synapse between nerve and muscle. Ach then binds to receptors on the muscle cells and causes their contraction through a rapid entering of calcium ions in their cytoplasm [12].

Some peptides possess structural similarities in the aminoacidic sequence of SNAP-25 and therefore compete for its binding sites on the SNARE complex, thus leading to its destabilization and consequent inhibition of Ach release at nervous endings [13]. Such a mechanism of action is the same as that displayed by Botulinum neurotoxins whose use is limited because of their high toxicity. Among the peptides interfering with the formation of the SNARE complex, the first to be introduced in dermatology was acetylhexapeptide-3 whose sequence is Ac-Glu-Glu-Met-Gln-Arg-Arg-NH2 (Argireline®, Lipotec SA, Barcelona, Spain). This peptide has been claimed to prevent the release of Ach, resulting in a significant reduction of wrinkles and improvement of skin mechanical properties as assessed in randomized, double-blind, placebo-controlled studies [14-17]. Very recently Aruan et al. tested a cream containing acetylhexapeptide-3 in a randomized, double-blind, placebo-controlled trial conducted on 21 women with crow's feet [18]. The subjects were treated for 8 weeks with acetylhexapeptide-3, which showed to be effective in treating eye-area wrinkles.

Following the introduction of Argireline® in dermatology, other peptides sharing the same anticholinergic action were identified and marketed, such as acetyl octapeptide-3 (Snap-8, Lipotec SA, Barcelona, Spain) corresponding to Ac-Glu-Glu-Met-Gln-Arg-Arg-Ala-Asp-NH2. This peptide was investigated in an open-label clinical trial conducted on 20 women using a formulation in which it was combined with palmitoyl tripeptide-5 (Pal-Lys-Val-Lys-OH) [19]. After 12 weeks of treatment, the test product reduced wrinkle depts in the periorbital area by 26% as compared with the pretreatment baseline. According to the authors, this effect was likely attributable to octapeptide-3, although its role could not be assessed individually. As mentioned, the test product also contained palmitoyl tripeptide 5. This peptide mimics the sequence located in thrombospondin 1, a protein reported to indirectly stimulate the production of collagen [20] and inhibit the expression of metalloproteases [21].

Some biomimetic peptides have been claimed to interfere with the cholinergic system by behaving as competitive antagonists of

Ach at the post-synaptic level, thus producing muscle relaxation with a mechanism of action different from that of Argireline®. Pentapeptide-3 (Vialox®), whose sequence is Gly-Pro-Arg-Pro-Ala-NH2, belongs to such a family of peptides [22]. According to its inventors, this peptide was designed to mimic snake venom. Similarly, tripeptide-3 (Syn-Ake®, Pentapharm Ltd, Basel, Switzerland), corresponding to β-Ala-Pro-Dab-NH-Bn, mimics the effect of waglerin-1, a peptide found in a viper [23] acting as a competitive antagonist of Ach. Unfortunately, there are no available published preclinical or clinical studies proving the efficacy of these two peptides.

An alternative approach to wrinkle lifting consists in the use of biomimetic peptides mimicking opioid peptides (endorphins, enkephalins, and dynorphins), all acting as agonists of specific G protein-coupled receptors. Opioid receptors can be divided into three subtypes: μ , δ , and κ receptors. Endorphins are more potent at μ and δ receptors, enkephalins bind preferentially to the δ receptor, whereas dynorphins are provided with the highest affinity for the κ receptor [24]. Binding of opioids to their receptors triggers several transduction pathways which ultimately lead to the activation of the potassium channels and deactivation of the calcium channels of the postsynaptic membrane, thus determining hyperpolarization [25]. Opioid receptors are expressed in different skin cells, including keratinocytes, melanocytes, hair follicles, immune cells, and peripheral nerve fibers [26,27]. Opioid peptides inhibit the release of Ach in the peripheral nervous system by interacting with their specific receptors located on cholinergic fibers. At the level of the neuromuscular plate, activation of the opioid receptors reduces the release of Ach with consequent downstream muscle relaxation [26]. Peptides mimicking endogenous opioid peptides have been developed as wrinkle-lifting agents thanks to their indirect anticholinergic activity on facial muscles.

Pentapeptide-18 corresponding to the sequence Tyr-Ala-Gly-Phe-Leu-OH, was the first to be characterized and introduced in the market as an anti-aging agent with the tradename of Leuphasyl® (Lipotec SA, Barcelona, Spain). Like enkephalins, pentapeptide-18 inhibits the release of Ach in the synaptic cleft. An open-label study evaluated the efficacy of pentapeptide-18 in reducing wrinkles on 20 volunteers applying formulations of different concentrations on their face for 2 months. The 2% formulation decreased wrinkles by 35% and 28% in the frontal region and, respectively, in the periorbital zone [28].

Recently, we described the clinical assessment of a cream containing 4% SH-pentapeptide-5, marketed as Peptilift (Kalichem Srl, 25086 Rezzato, Italy) which was designed as an endorphin-like peptide [29]. This randomized, patient-blind, placebo-controlled study was conducted on 40 women who were equally divided into two groups depending on whether they received the SH-pentapeptide-5-containing cream or the vehicle lacking active ingredients as the placebo. Instrumental measurements showed that the skins of the volunteers applying SH-pentapeptide-5 were found firmer and more elastic as compared with those treated with placebo. High-resolution digital images captured for all subjects at baseline and after completion of the treatment revealed a significant improvement in face roughness in the group treated with SH-pentapeptide-5.

Conclusion

Over the last twenty-five years the number of peptides used as anti-aging agents has grown considerably, thus bringing a wide range of innovative cosmetic products to the market. In this minireview we have highlighted some of the main achievements in the design and development of biomimetic peptides acting as inhibitors of neurotransmitters. All of them share the mechanism of action with their natural counterparts while offering the advantage of featuring a low molecular weight, a suitable lipophilicity for skin permeation, and an excellent tolerability profile. Some of these commercially available peptides have been clinically evaluated for their efficacy in reducing wrinkles whereas a not negligible number of them still await a scientific validation of the effects claimed by their manufacturers. Almost all the peptides tested in clinical studies were combined with additional active ingredients, such as vitamins and herbal extracts, contained in the same topical formulation. The contributions of such extra ingredients to the clinical efficacy of the formulation cannot be ruled out, thus complicating a precise estimate of the precise effects attributable to the single biomimetic peptide. Novel peptides should be characterized whenever possible for their lipophilicity by measuring partition coefficients similarly to what is done for drug-like small molecules. It would also be desirable to assess and disclose their capability of penetrating skin through ex vivo experiments using human skin, animal skin or artificial skin models. Overall, literature offers some valuable examples of biomimetic peptides disrupting cholinergic transmission which have proved to be effective and safe for daily use as topical anti-aging agents.

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Conflict of interest

No Conflict of Interest.

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