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Editorial

Peptides and Their Mechanisms of Action in the Skin †

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† I dedicate this editorial to my cosmetology students. Anna Waszkielewicz

1. Introduction

The skin, the largest organ of the human body, not only has a protective function, but also plays a key role in aesthetics and health. It is a physical barrier separating us from the outside world, but at the same time a living tissue in which complex biological processes constantly take place [1]. Over the years, under the influence of internal and external factors, such as UV radiation, from which it protects us thanks to pigment cells, oxidative stress or hormonal changes as well as gravity, the skin loses its elasticity, firmness and ability to regenerate [2]. Natural skin aging contributes to reduced production and increased degradation of extracellular matrix proteins, such as collagen, fibronectin, elastin and laminin, which are the frame for skin cells [3]. The aging process, inevitable and visible, is becoming a challenge that both scientists and cosmetology specialists struggle with. It is, however, a motivation in the search for solutions for maintaining the youthful appearance of the skin, where more and more attention is being paid to modern active ingredients such as bioactive and biomimetic peptides, which offer unique possibilities of supporting natural repair processes and counteracting the signs of aging [4].

2. An Overview of Publications and Intellectual Property Literature

Unique properties of peptides are valued due to their participation in the regulation of homeostasis, stress, immunity, defense against pathogens and regeneration [5]. In terms of cosmetological use, the advantages of peptides include non-invasiveness, possibility of self-application (no injection) and higher safety comparing to botox. On the other hand, their disadvantages are the time needed for visible effect measured in weeks (except for Syn-Ake), lability of structure, and of course, price resulting from manufacturing and storage conditions.

Bioactive peptides, usually consisting of 3–30 amino acids, come from natural proteins and act as signaling molecules or substrates involved in various biological processes. They are short chains of amino acids (up to 50), connected by peptide bonds, which distinguishes them from proteins (100 or more amino acids) [4,6]. Peptides occur in our body and are produced by various tissues, fulfilling regulatory, transporting, signaling, immune response, hormone and many other roles, but some of the peptides called biomimetic are produced synthetically [7].

Peptides can also be classified according to the division into signal peptides, neurotransmitter peptides, enzyme inhibitor peptides and carrier peptides [6].

2.1. Signal Peptides

Signal peptides are active substances that can counteract the skin aging process by stimulating fibroblasts to act. As a result, there is an increased biological response, such as increased production of collagen, elastin, fibronectin, glycosaminoglycans, and proteoglycans. These peptides can also act as growth factors by activating protein kinase C, which

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plays a key role in cell growth and migration [3]. Signal peptides are used either to enhance metabolism of fibroblasts or fasten hair growth.

Carnosine (β-(*Ala–His*)) is a dipeptide which is also used as a food supplement. Its wound healing activity is a feature making it a cosmetic, especially for eye cream, because *stratum corneum* around the eyes is the thinnest [8]. It has been bound with palmitic acid into palmitoyl-carnosine in order to enhance permeation through *stratum corneum* so that the compound can be effectively used on the whole face (Figure 1).

Figure 1. Chemical structure of palmitoyl-carnosine. Palmitoyl group is marked red.

Palmitoyl tripeptide-3 (Syn-Coll, (*Pal–Lys–Val–Lys*) bistrifluoracetate) stimulates synthesis of collagen, also through TGF-β [9].

A palmitoylated peptide is Pal-KTTKS (Matrixyl, palmitoyl pentapeptide)—Lys-Thr-Thr-Lys-Ser. KTTKS is a procollagen 1 fragment and it stimulates synthesis of collagen, elastin and hyaluronic acid [10]. Another peptide, also patented by Sederma, Pal-GQPR (palmitoyl 7-tetrapeptide, Matrixyl 3000)—Gly-Glu-Pro-Arg, stimulates collagen synthesis by fibroblasts. Moreover, it inhibits production of interleukin IL-6 resulting in anti-inflammatory effect. $Pal-KMO_2K$ under the tradename MATRIXYL Synthe-6 (MO_2 corresponding to a dioxygenated methionine) [9].

VGVAPG constitutes a fragment of elastin (elastin-derived peptides EDPs) and is a chemotactic signal peptide for fibroblasts. EDPs initiate human mesenchymal stem cells (hMSCs) differentiation into more tissue-specific cells [11]. It also decreases in the level of reactive oxygen species (ROS) [12].

Certain peptides have been developed for stimulation of hair growth. For example, tripeptide-1 combined with biotin (vitamin H)—biotinyl GHK in Lash Accelerator—or a preparation preventing hair loss Procapil. The longest of this group is KGF (Keratin Growth Factor) used in EyeLash Enhancer, containing 164 amino acids.

Leuphasyl—pentapeptide-18 (*Tyr–D–Ala–Gly–Phe–Leu*) inhibits secretion of sebum. A response for androgenic hair loss may be acetyl-tetrapeptide-3 [13]. It also decreases neuronal excitation by imitating activity of enkefalins [14].

The tradename Renokin, includes decapeptide-10, oligopeptide-54 (CG-Nokkin), decapeptide-18, acetyl decapeptide-3, and oligopeptide-42 which promote hair growth [15].

There are also peptides preventing hair greying: α-melanocyte stimulating hormone (acetylhexapeptide-1, $Ac–Nle–Ala–His–D\text{-}Phe–Arg–Trp–NH_2$) [16,17] Melitane)-$\alpha$-MSH biomimetic peptide. On the other hand, PTP-20 (Palmitoyl tetrapeptide-20, Greyverse) was developed for the use of MC1 receptor agonist and it increases quantity of melanin in human melanocyte culture [18].

Aquashine PTX 4 contains decapeptide-29, oligopeptide-62, acetyl decapeptide-3, oligopeptide-24, oligopeptide-72, oligopeptide-34, oligopeptide-51 with sodium hyaluronate [19]—the peptide ingredients of the preparation have been patented for all possible uses in the skin. *Ac–Asp–Val–Lys–Tyr–OH* increases the expression of fibulin-5, increases synthesis of type I collagen as well as elastin through overexpression of various genes [20].

2.2. Enzyme Inhibitors

An example of peptides that are direct and indirect enzyme inhibitors are rice and soy peptides. Soy peptides obtained from soy are proteinase inhibitors [3]. Rice peptides,

on the other hand, are natural proteins that inhibit the action of matrix metalloproteinases and stimulate the expression of the gene responsible for the synthesis of hyaluronan 2 in keratinocytes [21].

2.3. Neurotransmitter Peptides

An example of a peptide that inhibits neurotransmitters is acetyl hexapeptide-8 (Argireline, *Ac–Glu–Glu–Met–Gln–Arg–Arg–*NH_2) (Figure 2), which has an effect similar to botulinum toxin. It inhibits docking of vesicles in neuromuscular synapses, which reduces secretion of acetylcholine to the synapse and as a consequence, the formation of wrinkles [19]. The structure was based on SNAP-25 protein. It reduces wrinkles, however, the effect is visible after nearly a month [22].

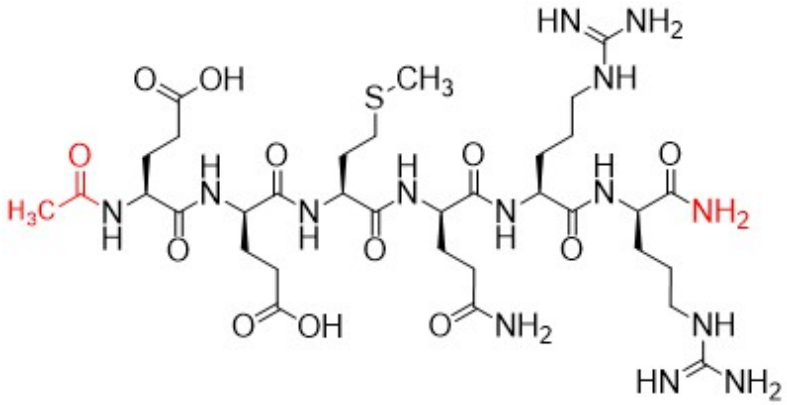

Figure 2. Chemical structure of argireline. Acetyl and amide groups are marked red.

SNAP-8—acetyl-octapeptide-3 $Ac - Glu - Glu - Met - Gln - Arg - Ala - Asp - NH_2$ (acetyl-glutamyl-heptapeptide-3) has the same mechanism of action as argireline [23].

Syn-Ake (β-Ala-Pro-GABA-benzylamide) represents reversible antagonism of N_m receptor and was designed on the basis of waglerin-1, temple pit viper (Tropidolaemus wagleri) venom. Waglerin-1 contains 22 amino acids and obviously is too large to get easily absorbed through stratum corneum. Syn-Ake has an immediate antiwrinkle effect and can be used directly before a party. On the other hand, this peptide is also added to cosmetics containing Argireline in order to fasten visibility of effects. Pentapeptide-3 (Vialox, Gly-Pro-Arg-Pro-Ala-NH2) is a competitive Nm antagonist. Moreover, is has sebostatic activity [14].

2.4. Carrier Peptides

The last type of peptide is carrier peptides, and in this case we will look at the copper peptide hidden in cosmetology under the name Copper Tripeptide-1. Gly-His-Lys (GHK, matricryptin) is the biological name of the tripeptide isolated from human plasma, showing a strong affinity for copper (II) ions, with which it forms a complex (GHK-Cu) spontaneously. Initially, it was identified as a growth factor for various mature cells, but more recent studies indicate its physiological role in wound healing and tissue regeneration. GHK-Cu directly supports wound healing and stimulates biological processes essential for tissue repair, such as angiogenesis, nerve development, and chemoattraction of key cells for the healing process (e.g. macrophages, monocytes, mast cells, capillary endothelial cells) [24]. Maquart et al. reported that GHK-Cu stimulates collagen synthesis in cultured fibroblasts, independent of the action of growth factors [25]. The presence of the GHK sequence in the α1(I) chain of human collagen suggests that this tripeptide may be released during the collagen production process. It is also very helpful in the wound healing process, where it supplies copper for matalloproteinase, hence its classification as a carrier peptide [6]. The copper peptide was initially confused with a growth factor, but Pickart et al. demonstrated that it has a stimulating effect on fibroblasts [26,27]. It reduces reactive

oxygen species (ROS) production, increases superoxide dismutase (SOD) activity while decreases TNF-α and IL-6 production through the suppression of NF-κ B, p65 and p38 MAPK signaling [28]. The tripeptide has been also subject to modification. Pal-GHK stimulates fibrillogenesis probably by activity on TGF-β [8]. Biotinyl-GHK is also capable of binding copper [29].

The proposed mechanisms of action refer to many compounds, and there are many more peptides, contained in preparations under registered names, as listed below, in alphabetic order [9,19]:

1. ActiMatrix: Peptide based mushroom Extract;
2. Actimp 1.9.3: Hydrolyzed Lupine Protein
3. Adifyline: Acetyl Hexapeptide-38
4. Aldenine: Hydrolized Wheat Protein, Hydrolized Soy Protein, Tripeptide- 1
5. Ascotide: Ascorbyl Phosphate Succinoyl Pentapeptide-12
6. BeauActive MTP: Hydrolyzed milk protein
7. Bio-Bustyl: Rahnella Soy Protein Ferment, Palmitoyl Oligopeptide
8. Biopeptide CL: Palmitoyl Oligopeptide
9. Biopeptide EL: Palmitoyl Oligopeptide
10. BONT-L-Peptide: Palmitoyl Hexapeptide-19
11. Caspaline 14: Hexapeptide-42
12. ChroNOgen: Tetrapeptide-26
13. ChroNOline: Caproyl Tetrapeptide-3
14. Colhibin: Hydrolyzed Rice Protein
15. Collaxyl: Hexapeptide-9
16. Cytokino: Hydrolyzed Casein, Hydrolyzed Yeast Protein
17. Decorinol: Tripeptide-9 Citrulline
18. Decorinyl: Tripeptide-10 Citrulline
19. Deepaline: Palmitoyl hydrolyzed Wheat Protein
20. Delisens: Acetyl Hexapeptide-46
21. DermaPep A350: Myristol Tripeptide-31
22. DermaPep A420: Myristoyl Tetrapeptide-6
23. Dermican: Acetyl Tetrapeptide-9
24. dGlyage: Lysine HCl, Lecithin, Tripeptide-9 Citrulline
25. Diffuporine: Acetyl Hexapeptide-37
26. Drieline: Yeast Betaglucan
27. Dynachondrine ISR: Hydrolized Soy Protein
28. ECM Moduline: Palmitoyl Tripeptide-28
29. ECM Protect: Tripeptide-2
30. Effipulp: Hydrolyzed Avocado Protein
31. Elhibin: Glycine Soja Protein
32. Extracellium: Hydrolyzed Potato Protein
33. Eyeseryl: Acetyl Tetrapeptide-5
34. Granactive AGE: Palmitoyl Hexapeptide-14
35. Inyline: Acetyl Hexapeptide-30
36. IP 2000: Trifluoroacetyl Tripeptide-2
37. Juvefoxo: Acetyl Hexapeptide-50
38. Kollaren: Tripeptide-1
39. Laminixyl IS: Heptapeptide
40. Leuphasyl: Pentapeptide-18
41. Liftline: Hydrolyzed Wheat Protein
42. Lipacide PVB: Palmitoyl hydrolyzed Wheat Protein
43. Lipeptide: Hydrolized Vegetable Protein
44. Marine Filling Spheres: Atelocollagen
45. Pentacare-NA: Hydrolyzed Wheat Gluten
46. Pep 4-17: Tetrapeptide-17

47. Pepha-Timp: Human oligopeptide-20
48. Peptamide 6: Hexapeptide-11
49. Peptide AC29: Acetyl Tripeptide-30 Citrulline
50. Peptide Q10: Pentapeptide-34 Trifluoroacetate
51. Peptide Vinci 01: Penta-decapeptide-1
52. Peptide Vinci 02: Hexapeptide-3
53. Peptiskin: Arginine/Lysine polypeptide
54. Preregen: Glycine soja (Soybean) Protein, Oxido Reductases
55. Preventhelia: Diaminopropionoyl Tripeptide-33
56. Prodejine: Yeast Extract
57. Prolixir S20: Dimer Tripeptide-43
58. Quintescine: Dipeptide-4
59. Raffermine: Hydrolyzed Soy Flour
60. Relistase: Acetylarginyltriptophyl Diphenylglycine
61. Renaissance: Hydrolyzed Wheat Protein, Palmitoyl Decapeptide-21, Decapeptide-22, Oligopeptide-78, Zinc Palmitoyl Nonapeptide-14
62. Regu-Age: Hydrolyzed Rice Bran Protein, Glycine Soja Protein
63. Ridulisse C: Hydrolyzed Soy Protein
64. Serilesine: Hexapeptide-10
65. Silusyne: Soybean (Glycine Soja) Oil, Lauryldimonium Hydroxypropyl Hydrolized Soy Protein, Acetyl Hexapeptide-39
66. SNAP-7: Acetyl Heptapeptide-4
67. Survixyl IS: Pentapeptide- 31
68. Syn-Glycan: Tetradecyl Aminobutyroylvalyl-aminobutyric Urea Trifluoroacetate
69. Syn-Tacks: Palmitoyl Dipeptide-5 Diaminobutyloyl Hydroxythreonine, Palmitoyl Dipeptide-6 Diaminohydroxybutyrate
70. Syn-TC: Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate, Palmitoyl Tripeptide-5, Palmitoyl Dipeptide-5 Diaminobutyroyl Hydroxythreonine
71. Syniorage: Acetyl Tetrapeptide-11
72. TEGO Pep 4-Even: Tetrapeptide-30
73. Telangyn: Acetyl Tetrapeptide-33
74. Telosense: Hydrolized Soy Protein, Hydrolized Yeast Protein
75. Thermostressine: Acetyl Tetrapeptide-22
76. Thymulen 4: Acetyl Tetrapeptide-2
77. TIMP Peptide: Acetylhexapeptide-20
78. Triactigen: Yeast Extract
79. Trylagen: Hydrolyzed Wheat Protein, Hydrolyzed Soy Protein, Tripeptide-10 Citrulline, Tripeptide-1

3. Conclusions

This review presents variability of mechanisms of action of various peptides used in cosmetology. It is worth mentioning that law referring to cosmetics ingredients is not as much restrictive as pharmaceutical law, therefore, we do not really know all the mechanisms, and disadvantages, as well as long term toxicity of these compounds. A few years ago it looked like these few compounds that have been described will be enough on the market, but patent laws encouraged cosmetology producers to search for new active peptides for which they may have their own patent and resulting from it monopoly. It is worth observing how this domain of cosmetological peptides evolves.

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