Review Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713
Pooja Bains, IJPRBS, 2016; Volume 5(6): 118-125 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

TOPICAL PEPTIDES FOR AGEING: POTENTIAL ROLE IN DERMATOLOGY

DR.POOJA BAINS

Assistant Professor, Dept of Skin & V.D, Sri Guru Ram Das Institute of Medical Sciences & Research, Sri Amritsar.

Accepted Date: 11/12/2016; Published Date: 27/12/2016

Abstract: Ageing is an inevitable ongoing process which is noticeable within all organs of the body and manifests itself visibly in the skin. A wide range of antiageing and antiwrinkle dermatological products are available .With the ongoing research for better antiageing and antiwrinkle products and the better understanding of skin homeostasis, the role of bioactive peptides in treatment of skin ageing is evolving. These drugs labelled as dermocosmetics have slowly paved their way in the treatment of skin ageing, melasma and hair growth, but there is still a long way to go before we can justify their role in dermatology. A number of clinical trials and in vivo and in vitro studies are present on peptides but there is a critical lack of scientific randomized control studies. Peptides are active ingredients in many new dermatological products ,so before prescribing, it is important to know about their potential and limitations so as to have realistic expectations .Till the time further research on topical peptide is conducted, we need to keep a judicious approach about their adjuvant role in rejuvenation of skin . The aim of this review is to analyse this newer generation of skin rejuvenation products: the synthetic peptides and their potential role in antiageing.

Keywords: peptides, synthetic, antiageing

PAPER-QR CODE

Corresponding Author: DR. POOJA BAINS

Access Online On:

www.ijprbs.com

How to Cite This Article:

Pooja Bains, IJPRBS, 2016; Volume 5(6): 118-125

INTRODUCTION

Topical Peptides for ageing: Potential role in dermatology

The proteins and peptides are involved in various aspects of skin structure and functioning as they modulate various biological processes in the dermis and epidermis. This is a new and growing field of skincare as the peptides hold a great potential to delay skin changes associated with ageing. To understand the role of peptides in skin ageing, we need to discuss the molecular mechanism of ageing and the action of peptides at molecular level.

Molecular mechanisms of skin ageing: At the biochemical and molecular level, a number of complex factors interplay which contribute to skin ageing. The growth factors and cytokine mediators alter the intercellular matrix and are responsible for changes in skin.[1] There is an increase in proteolytic activity with ageing which results in breakdown of proteins and an increase in free radical damage.

The various changes at molecular and biochemical level include:

a. Collagen loss: With ageing, there is a decrease in synthesis of collagen along with an abnormal glycation of collagen. Due to abnormal glycation, the advanced glycation end products (AGEs) i.e.end products of glycated collagen and proteins, are deposited on collagen and elastin tissue, making them stiffer and resistant to remodelling.[2] AGEs lead to enhanced oxidative stress and elaboration of proinflammatory cytokines. The resulting free radicals and cytokines lead to breakdown of collagen.[3]

b. Role of Proinflammatory cytokines: The immune system functions by protecting skin from pathogens and other environmental toxins, but at the same time, this activation of immune system can lead to increase in pro inflammatory cytokines. These cytokines play a role in ageing as they result in cellular damage by causing inflammation and generation of reactive oxygen species.[4] Keratinocyte and dermal derived cytokines may play a role in melanocyte proliferation and cause pigmentation in cutaneous ageing. The aged keratinocytes cause increased secretion of IL-1 alpha resulting in hyperpigmentation with ageing.[5]

c. Role of Growth factors: A growth factor is a naturally occurring protein capable of stimulating cellular growth, proliferation, healing, and cellular differentiation. The epidermal growth factors (EGF) are secreted by keratinocytes and bind to the EGF receptors to induce keratinocyte proliferation. EGF is important in wound healing and regulation of keratinocyte differentiation. With ageing, decreased responsiveness of EGF receptors is seen, which lead to subsequent decrease in fibroblast migration and proliferation.[4] Transforming growth factor (TGF) beta has the ability to promote production of the extracellular matrix and serves as a

growth factor for fibroblasts .There is a reduction in function of TGF beta with age, impairing the wound healing and collagen synthesis.[4]

d. Signalling peptides: The extracellular matrix has self-regenerating and repair capacity by releasing peptides. The repair function occurs by protein synthesis and cellular regeneration. The peptides which are released by the ECM to cells are called signalling peptides. This repair mechanism is altered in aged skin.[6]

Bioactive peptides: This is a family of biologically active regulators that are released after injury from the extracellular matrix (ECM) proteins, mainly- elastin, collagen, fibronectin and thrombospondin.[7] These first emergency response molecules are also called Matrikines. These bioactive peptides are usually small, containing between 3-8 amino acids. The break-up of collagen or elastin results in release of oligopeptide fragments of defined amino acid sequence, some of which have biological signalling activity. The collagen has chemotactic activity for fibroblasts and monocytes even after proteolysis which enhances the tissue repair process.[8] Thus, the debris pieces, generated as a consequence of the traumatic event, are employed to help in repairing the damage. The cellular effects of bioactive peptides are given in table 1.

Antiageing mechanisms of bioactive peptides:

- The biologically active peptides have a potential to augment and maintain synthesis of extracellular matrix proteins .[9]
- Peptides modulate dermal collagen synthesis via direct stimulation of collagen synthesis or decreasing degradation of collagen.[9]
- Few peptides are capable of inhibiting melanin synthesis by competitively inhibiting tyrosinase,the rate limiting enzyme in melanogenesis .[9]
- Neurotransmitter affecting peptides increase the threshold for muscle contraction at the neuromuscular junction resulting in muscle paralysis mimicking the effect of botulinum neurotoxin in reduction of wrinkles.[9]

The bioactive peptides including Palmitoylated tri, tetra-, penta- and hexapeptides, derived from collagen, immunoglobulin, laminin and elastin sequences are used in various antiageing products. There are innumerable peptides under trial, but in this article we will discuss only those peptides which have entered the domain of dermatologist's prescriptions.

1. Tetrapeptide 21 and 30: The tetrapeptide 21 contains Glycine-Glutamic acid-Lysine-Glycine (GEKG) and Tetrapeptide 30 contains Proline-Lysine-Glutamic acid-Lysine amino acids (PKEK). Tetrapeptide 21 is present in several human extracellular matrix proteins and has

demonstrated in vitro and in vivo capability of inducing collagen production at the transcriptional and translational levels ,hence improves skin elasticity and reduces skin roughness.[10] Tetrapeptide 30 acts by reducing keratinocyte induced activation of melanocytes thereby having role in melasma . [10]

2. Palmitoyl Tetrapeptide 7 (Pal GQPR) : This peptide (also called palmitoyl tetrapeptide3) has amino acid sequence containing Glycine Glutamine Proline Arginine. This peptide is a fragment of a natural circulating protein IgG which specially reduces the basal and UV radiation induced secretion of IL 6.[11] The cytokine IL 6 is known to cause glycation damage to collagen, elastin and other proteins resulting in a wrinkled, sagged and uneven skin texture which is reduced by this peptide.

3.Tripeptide1: This peptide, glycyl-histidyl-lysine (GHK),is a fragment of the alpha 2(1)chain of collagen, also found in a glycoprotein SPARC that is produced by endothelial cells at the site of injury by proteolysis.[12] This tripeptide acts as a stimulus for extra cellular matrix synthesis by a natural feedback mechanism.[13] It possesses a high affinity for copper ions and forms the complex GHK-Cu. GHK-Cu maintains a balance between ECM breakdown and synthesis by simultaneously modulating activity of different matrix metalloproteinases and stimulating anti-proteases.[12] In addition to improving transepidermal copper delivery and increasing collagen synthesis, GHK-Cu may also upregulate elastin production.[14] This is an added benefit which further explain the favourable cosmetic outcomes associated with this complex. The favourable properties of this peptide in improving wound healing, enhancing extracellular matrix proteins, skin repair, stimulation of blood vessel growth and role in antioxidant defence make it a promising ingredient in topical antiageing product.[12] GHK-Cu complex has proved to be non-allergenic and did not produce eye irritation.[12] Combination of Pal –GHK and Pal – GQPR is said to have a synergistic effect.[11]

4. Palmitoyl pentapeptide-3: It is also called palmitoyl pentapeptide-4 and palmitoyl oligopeptide. It is one of the first oligopeptides to be developed as a cosmeceutical agent. This pentapeptide contains Lysine-Threonine-Threonine-Lysine-Serine (KTTKS), a fragment derived from the carboxyl-terminus of type I procollagen .[15] This oligopeptide when conjugated to the 16-carbon fatty acid, palmitate, to create palmitoyl pentapeptide (pal-KTTKS) results in more effective delivery across skin relative to pentapeptide alone.[16] A double blind, vehicle-controlled study done on 49 women with 3 parts per million of Pal-KTTKS twice a day application for 4 months showed a 13% reduction in skin roughness ,27% decrease in wrinkle depth and 36% decrease in wrinkle volume.[17] Pal KTTKS in comparison to retinol has an advantage of having equal efficacy without the side effects.[16]

5. Nonapeptide 1: It is also called Melanostatin 5 and consists of peptides Arginine, Lysine, Methionine, Phenylalanine, Proline, Tryptophan and Valine. It is a skin lightening peptide, derived from the melanocyte stimulating hormone. It has a high affinity for the MC1-R and competes with alpha MSH to bind the receptor and blocks it preventing further production of tyrosinase, resulting in melanin synthesis inhibition, hence reducing the hyperpigmentation. [18]

6. Acetyl hexapeptide-3: It is also called Acetyl hexapeptide 8. It is a synthetic peptide derived from the N-terminal domain of the protein SNAP-25 containing Ac-Glu-Glu-Met-Gln-Arg-Arg-NH2. This neurotransmitter inhibitor peptide functions by blocking catecholamine release by interfering with the formation of the ternary SNARE complex in chromaffin cells.[19] It has shown to have similar potency as Botulinum toxin with respect to neurotransmitter release, but displayed lower efficacy. This peptide is well tolerated with no irritation even at high doses. This peptide has been used in dosage of 5% to reduce deep lines or wrinkles in the forehead or around the eyes.[20]

7.Acetyl octapeptide 3 (SNAP 8) : This peptide is an elongation of acetyl hexapeptide 3, a mimic of the N terminal end of SNAP-25, that competes with the native protein for a position in the SNARE complex , hence destabilizing it ,thus the vesicle cannot release neurotransmitters efficiently and therefore muscle contraction is attenuated, preventing the formation of lines and wrinkles.[19]

Advantages of synthetic peptides:

a. They can be modified in innumerable ways.

b. The various physical properties including potency, solubility, permeability can be regulated by aminoacid substitution

c. As peptides tend to clear from blood stream rapidly due to enzyme degradation, minimal dosage toxicities can be expected.

d. They are highly specific.

e. Oligopeptides which mimic effect of botulinum neurotoxin are much less neurotoxic and therefore safer for patients.

f. The very high potency of the peptides compensate for their cost and make it possible to employ them at efficient level in all types of skincare formulations.

Disadvantages and pitfalls in using synthetic peptides:

a. Short plasma half-lives because of rapid renal clearance and enzymatic degradation hence cannot be used in conditions where prolonged action is required.

b. High cost of therapy

c. Proteins and peptides pose challenges for passive transdermal delivery because of the fact that they may be charged at physiological pH.

d. The larger the peptide (beyond six or seven amino acids), the less likely it is to reach the deeper layers of the skin.

e. The peptides have limited chemical stability, so chances of hydrolysis in topical formulations may occur.

f. In the absence of randomized clinical trials, the efficacy of these compounds is often questioned by dermatologists.

CONCLUSION:

The aim of this review is to discuss the current advances in cosmeceuticals and the expanded spectrum of synthetic bioactive peptides in antiageing products. We have made an attempt to enumerate the more commonly encountered peptides being used nowadays in skin rejuvenation. In present scenario, all the pharmaceutical companies are launching new products with bioactive peptides as the key ingredients and as dermatologists we need to make evidence-based decisions about these products. There is a thin line between the hype and optimism associated with the bioactive peptides hence there is need for further randomized controlled studies. The beneficial effects of synthetic peptides will provide yet another tool in the treatment armamentarium of dermatologists actively seeking to improve patient care and outcomes.

Table 1:The cellular effects of bioactive peptides at various level:

1. **Stimulates collagen1, fibronectin, and hyaluronic acid synthesis.**
2. **Stimulates cell migration,fibroblast proliferation and scaffolding.**
3. **Down regulates IL 6 in resting and inflamed cells.**
4. **Promotes endothelial cells migration and tubulogenesis.**
5. **Increases synthesis of dermatan sulphate and chondroiton sulphate.**
6. **Inhibits tyrosinase and attenuates melanin synthesis.**

REFERENCES

1. Quiroga RM. Antiageing medicine as it relates to dermatology.In: Cheryl M Burgess, editor. Cosmetic dermatology. Germany: Springer ; 2005.p. 2-3.

2. Baumann L,Saghari S, Weisberg E,editors.Cosmetic Dermatology.2nd ed. New York:Mc Graw Hill;2009.p-9.

3. Goh SY, Cooper ME. Clinical review: The role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab. 2008 Apr;93(4):1143-52

4. Baumann L,Saghari S, Weisberg E,editors.Cosmetic Dermatology.2nded.New York:Mc Graw Hill;2009.p-23-24

5. Okazaki M, Yoshimura K, Uchida G, Harii K. Correlation between age and the secretions of melanocyte-stimulating cytokines in cultured keratinocytes and fibroblasts. Br J Dermatol.2005 Dec;153 Suppl 2:23-9.

6. Fields K, Falla TJ, Rodan K, Bush L. Bioactive peptides: signaling the future. J Cosmet Dermatol. 2009 Mar;8(1):8-13.

7. Jacek Arct, Matgorzata Gulba. Matrikines in skincare. Pol J Cosmetol 2014, 17(2): 103-107

8. Senior RM, Griffin GL, Mecham RP, Wrenn DS, Prasad KU, Urry DW. Val-Gly-Val-Ala-Pro-Gly, a repeating peptide in elastin, is chemotactic for fibroblasts and monocytes.J Cell Biol. 1984 Sep;99(3):870-4

9. Reddy B, Jow T, Hantash BM. Bioactive oligopeptides in dermatology: Part 1. Exp Dermatol. 2012 ;21(8):563-8

10. Mentel M, Schild J, Maczkiewitz U, Koehler T, Farwick M.Innovative Peptide Technologies for Even,Young and Healthy Looking Skin. SOFW-Journal.2012 :22-33

11. Karl Lintner. Peptides and proteins.In : Draelos.ZD,editor. Cosmetic Dermatology: Products and Procedures. Oxford, UK. Wiley-Blackwell ;2010.p.295

12. Pickart L, Margolina A .GHK–Copper Peptide in Skin Remodeling and Anti-Aging. SOFW-Journal 2010 :1-9

13. Lintner K, Peschrad O. Biologically active peptides: from a laboratory bench curiosity to a functional skin care product. Int J Cosmet Sci. 2000;22(3) :207-218

14. Loren Pickart, Vasquez-Soltero JM, Margolina A. The Human Tripeptide GHK-Cu in Prevention of Oxidative Stress and Degenerative Conditions of Aging: Implications for Cognitive Health.Oxid Med Cell Longev.2012

15. Katayama K, Armendariz-Borunda J, Raghow R, Kang AH, Seyer JM. A Pentapeptide from Type I Procollagen Promotes Extracellular Matrix Production. J Biol Chem. 1993 May 15; 268(14):9941-4.

16. Tsai TC, BM Hantash. Cosmeceutical Agents: A Comprehensive Review of the Literature.Clin Med: 2008:1–20.

17. Guttman, C. Studies demonstrate value of procollagen fragment Pal-KTTKS. Dermatology Times. 2002; 23(9):68.

18. Gupta VK, Tuohy MG(editors) Biotechnology of Bioactive Compounds: Sources and Applications.Oxford,U.K: Wiley-Blackwell;2015.680.

19. Farage MA,Miller KW, Maibach HI(editors).Textbook of Aging Skin.Berlin: Springer;2010.1112.

20. Blanes-Mira C, Clemente J, Jodas G, Gil A, Fernández-Ballester G, Ponsati B et al. A synthetic hexapeptide (Argireline) with antiwrinkle activity. Int J Cosmet Sci. 2002 Oct;24(5):303-10