Perplexing Peptides Unraveled

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Proteins are the most allergenic substances when placed on the skin. For this reason, cosmetics avoided the use of proteins for many years. Probably the first protein used on the skin was hydrolyzed collagen derived from the heating of bovine skin. This protein was added to hair conditioners and skin moisturizers for its ability to function as a humectant to hold water. The use of hydrolyzed collagen revolutionized skin care and hair care in the 1980s. More recently, with advancements in protein chemistry, engineered molecules can be created that mimic functioning structures within the body. Since proteins are too big to penetrate the skin barrier, engineered peptides made of carefully selected amino acids are synthesized to potentially enter the stratum corneum theoretically affecting epidermal and dermal functioning.

Peptides are the cellular messengers of the body that allow the modulation of receptors, activate enzyme release, and regulate the production of proteins. Peptides are present in many of the new-generation cosmeceuticals. They are considered safe when applied topically, because peptides are ingested on a regular basis when consuming meat. Allergic reactions to cosmetic topical peptide formulations have not been reported to date, thus increased use of peptide technology in moisturizers is expected in the future. This article examines the peptide families that currently are in use and looks at specific peptides as examples of each family.

Peptide Families

Peptides are formed from amino acids that are selected by the protein chemist to achieve a specific functional goal. The peptide families that have been presently identified are listed in the Table. The first peptides introduced into the wound-healing marketplace were carrier peptides, which were then adapted to the anti-aging skin care market. From the carrier peptides, the next development was signal peptides designed to mimic a natural body structure and turn on or off production of an endogenous protein. Neurotransmitter peptides were then developed that interrupted acetylcholine release. Finally, enzyme-modulating peptides that directly or indirectly inhibit enzyme functioning were produced. This discussion now turns to specific examples of each of these peptide families that presently are in marketed cosmeceutical preparations.

Carrier Peptides

The first commercialized peptides were carrier peptides. These peptides were designed to hook to another ingredient and facilitate transportation of the agent to the active site. The first carrier peptide was designed to deliver copper, a trace element necessary for wound healing. From a wound-healing application, a peptide known as GHK-Cu (glycine, histidine, lysine, and copper) was commercialized into a line of skin care products designed to minimize the appearance of fine lines and wrinkles. GHK-Cu is composed of glycine, histidine, and lysine hooked to copper and was found to induce the proliferation of dermal keratinocytes. GHK was originally isolated from human plasma and then synthetically engineered.

Signal Peptides

The largest peptide family currently used in marketed cosmeceuticals is signal peptides. Signal peptides stimulate the production of collagen, elastin, fibronectin, proteoglycan, and glycosaminoglycan, which create the appearance of younger-looking skin. The most popular signal peptide is palmitoyl pentapeptide-3, (Matrixyl, Olay Regenerist). Palmitoyl pentapeptide-3, abbreviated Pal-KTTKS, is composed of the amino acids lysine, threonine, and serine. It is a procollagen type I fragment demonstrated to stimulate the production of collagen types I, III, and IV in vitro. It is used in a low concentration of 4 ppm, because it theoretically acts as a signal whereby one molecule has a cascading

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The author reports no conflict of interest in relation to this article.

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Peptide Families

- Carrier peptides
- Signal peptides
- Neurotransmitter peptides
- Enzyme-modulating peptides

effect. The idea is to present the body with procollagen fragments that will down-regulate the production of collagenase thereby increasing dermal collagen and minimizing the appearance of aging.

Neurotransmitter Peptides

Neurotransmitter peptides function by inhibiting the release of acetylcholine at the neuromuscular junction. They are similar to botulinum toxin in that both selectively modulate synaptosomal-associated protein of 25kDa (SNAP-25). Botulinum toxin type A proteolytically degrades SNAP-25 while acetyl hexapeptide-3, a neurotransmitter peptide, mimics the N-terminal end of the SNAP-25 protein that inhibits the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex formation. When applied topically, acetyl hexapeptide-3 (Argireline, Centerchem) supposedly functions to relax muscles, much like a weak short-lived botulinum toxin, by inhibiting vesicle docking through prevention of the SNARE complex formation. This muscle relaxation reduces the appearance of facial wrinkles.

A second commercialized neurotransmitter peptide is pentapeptide-3 (Vialox, Centerchem). Pentapeptide-3 is a competitive antagonist at the acetylcholine receptor. It also reduces muscle contraction and theoretically the depth of wrinkles on the face.

Enzyme-Modulating Peptides

Enzyme-modulating peptides directly or indirectly inhibit the function of a key enzyme in some metabolic process. Many of these enzyme-modulating peptides are extracted from botanical sources rather than engineered through protein chemistry. Soy proteins, already used in cosmeceuticals for the reduction of pigmentation and the inhibition of hair growth, possess another peptide that inhibits the formation of proteases. Rice proteins possess a peptide that inhibits matrix metalloproteinase activity. These naturally occurring peptides are used in cosmeceutical facial moisturizers in combination with the previously discussed synthesized peptides.

Summary

Peptides can be perplexing to the uneducated dermatologist, but once it is understood that they are naturally occurring or synthetic, biologically designed combinations of amino acids, the puzzle comes unraveled. The intent of the peptide chemist is to influence cellular communication by exposing the skin to mimics of naturally occurring amino acid sequences. While the effect of peptides easily can be demonstrated in Petri dish cultures of fibroblasts or muscle cells, it is much harder to assess the cosmeceutical value of topical peptides for human facial application. Almost all peptide formulations contain a mixture of robust, moisturizing ingredients. It can be difficult to determine whether the improvement in skin smoothness and reduction in facial wrinkles is due to the moisturizing abilities of the formulation or the addition of the peptide. In some regards, because cosmeceutical is a fancy name for cosmetics, as long as the consumer is pleased with the effect of the facial cream and purchases another container, the product is a success.

In dermatology, we want to link cause-and-effect to a specific ingredient. Indeed this should be our quest as skin scientists. However, double-blind, placebo-controlled studies are hard to conduct in the moisturizer realm because the vehicle formulation without the peptide may still produce skin improvement. This is why many cosmeceutical moisturizer tests are performed against the current market leader as a control. The goal is to show that the new peptide-containing finished formulation performs better than a presently marketed cream. Indeed the peptide-containing moisturizer may be better, but the superiority cannot be totally attributed to the peptide alone. This is a key distinguishing characteristic of the cosmetic realm from the drug realm.

It is important to recognize that peptide chemistry is yet in its infancy. Peptides hold the promise to modulate much of the functioning of the skin, but the details remain perplexing. This article has unraveled some of the confusion regarding peptides by organizing them into families and presenting examples of peptides in current use. The dermatologist should closely watch this family of cosmeceutical ingredients as their true potential has not yet been fully realized. ■

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