THE SCIENCE SUPPORTING SKINCEUTICALS RETINOL PRODUCTS

ABSTRACT

Retinol (vitamin A) and its natural and synthetic analogs are collectively known as retinoids. Retinoid research has been conducted for nearly a century and has yielded comprehensive findings regarding the importance of vitamin A as a nutrient, as well as the biological activities and pharmacological profiles of the various retinoids, most eminently retinol (ROL) and retinoic acid (RA). Drugs based on retinoids are now available for the treatment of psoriasis, acne and other dermatologic conditions related to keratinization. Medical research indicates that retinoic acid is beneficial to maintain youthful skin and to repair damage caused by UV exposure or intrinsic aging. Retinol is converted to retinoic acid once applied to the skin, but is without the prohibitive irritation potential of the latter. Studies show retinol as a viable solution for combating skin aging and problematic skin when delivered in a stable formulation at high concentrations.

BACKGROUND

Retinol has long been known as an important nutrient involved in a wide variety of functions from embryonic development to cell differentiation and vision. Deficiency of dietary vitamin A results in generalized xerosis, hyperkeratosis and squamous metaplasia of mucous membranes. ROL is the natural, diet-derived vitamin A, though the collective term also includes its metabolites retinal and retinoic acid. All three are part of a greater family generally referred to as retinoids. Grouped under this umbrella are not only the natural retinoids: retinol, retinal, and retinoic acid, but also the many synthetic analogs that have been researched and developed since the significance of vitamin A and all retinoids was discovered in the early 1920s.

HISTORY OF RETINOID RESEARCH

The importance of retinoids in dermatology dates back to Wolbach and Howe in 1925, who identified epidermal changes as abnormal keratinization in vitamin A deficient animals. These observations were followed by numerous studies focused on the metabolism and pharmacological action of retinoids in the skin. Investigations regarding the effect of topical retinol in the early 1960s (Kligman, Stuttgen) were unsuccessful due to ROL instability. These difficulties have recently been overcome by the creation of formulation technology that largely prevents the degradation of retinol due to light and heat exposure.[1] The difficulties encountered in the 1960s did lead to the concentration of research activities on retinoic acid and the development of other retinoids, consequently, the establishment of retinoid drugs for various skin diseases. These medicinal products are generally classified into different generations of retinoid development: The first generation comprises trans-retinoic acid or tretinoin (Retin-A®) and 13-cis-retinoic acid or isotretinoin (Accutane®), products effective for the treatment of acne. Etretinate and acitretin (Tegison and Soriatane) are second generation retinoid-based drugs and are used primarily for the treatment of psoriasis. A third generation still in experimental stage is arotenoids, possibly beneficial in the application of some cancer therapies.[2] Each retinoid has its own profile of pharmacological properties that determine its usefulness in clinical dermatology or oncology. In addition to existing clinical research, researchers found that retinoids can have a positive effect on intrinsic as well as photoaging symptoms as they relate to the skin.

GENERAL METABOLISM AND TRANSPORT OF NATURAL RETINOIDS

Retinol (natural vitamin A) is obtained from the diet either directly from foods such as fish oil and liver or indirectly in the form of beta-carotene, which with the help of enzymes is then converted to retinol for membrane transport. Retinol can be converted to retinoic acid for target cell delivery or converted to retinyl ester (RE) for storage.

Retinol binds with specific retinol-binding proteins (CRBP-I, CRPB II). These proteins facilitate the transport inside the cell, and are also believed to protect the molecule from non-specific oxidation. After the enzymatic conversion of the ROL molecule to RA, RA binds to the cellular retinoic acid binding molecule CRABP (CRABP-I, CRABP-II) and is transported from the cytoplasm to the nucleus. From there, it exerts its effect on the target cells by activating the retinoid receptors known as RA receptors (RARs) and retinoid X receptors (RXRs). These receptors contain domains that bind to specific DNA sequences, RA response elements (RARE), and function to enhance or reduce gene transcription.[3, 4] In human skin and dermal fibroblasts, it is cellular retinoic acid binding protein II (CRABP-II) mRNA that is selectively induced by all-trans retinoic acid.[5]

Note: Of the natural vitamin A compounds (retinol, retinal, retinoic acid, retinoic ester), only RA is biologically active.

RETINOIDS AND SKIN

The skin is formed by two basic layers: the epidermis, composed of keratinocytes in different stages of growth and differentiation, and the dermis, whose major cellular constituents are fibroblasts, which synthesize the fibrous component of the dermal connective tissue, i.e. collagen and elastin fibers, as well as other extracellular matrix components, such as fibronectin and laminin. Researchers suggest that cutaneous aging results from the interplay of extrinsic damage by UV radiation, intrinsic increases in collagen-degrading matrix metalloproteinases (MMPs) and decreased collagen synthesis. Numerous large-scale, double-blinded and placebo-controlled trials have shown the efficacy of topical tretinoin in the treatment of photoaging. However, as tretinoin remains a prescription drug, and in addition has a high irritation potential, over-the-counter products mainly use retinol and retinyl palmitate.

RETINOL RESEARCH

Researchers believe that retinol plays an important role in countering aging mechanisms described above. A study utilizing human skin samples found that topical 1% retinol inhibits the increase in metalloproteinases and stimulates collagen synthesis in both intrinsically aged and photoaged skin.[6] Varani et al. also used tissue specimens to show that retinol may be able to restimulate fibroblast growth potential, which seems to decrease with increasing age. Further, Kang et al. showed that topical retinol does increase epidermal thickness in human skin, but without the irritation of RA.[7] The above studies show that concentrations of 1% retinol produced results equivalent to prescription strength retinoic acid. Evidence for the effectiveness and biological activity of the ester form of vitamin A, retinyl palmitate, is sparse and no studies address clinically relevant findings in skin aging. Further, in mice, retinol stores in the epidermis were partially UVB resistant, while retinyl esters were not.

CONCLUSION

Retinoids are among the most prescribed and recommended classes of agents in the dermatologic arsenal. Decades of research have led to versatility in use of these products. Studies demonstrating corrective benefits such as cell regeneration, exfoliation, and dermal collagen synthesis suggest an important role for topical retinoids in counteracting the effects of photoaging. Although still in the early stages of research, retinol is a prominent agent among retinoids for combating skin aging as well as problematic skin. Factors determining the efficacy of retinol are concentration, stability, encapsulation method, and formulation. Results from various studies show retinol, when properly formulated, to be an effective topical treatment preferred to other retinoids due to its tolerability.

REFERENCES

1 Kligman L, Gans E. Re-emergence of topical retinol in dermatology. *J of Dermatological Treatment* 2000; 11: 47-52(6)

2 Neumann, Martino. Systemic and topical drugs for aging skin. *Journal of Drugs in Dermatology* 2003.

3 Roos T, Jugert K, Merk H. Bickers D. Retinoid metabolism in the skin. *Pharmacological Review* 1998; 50:315-33

4 Ross AC. Overview of retinoid metabolism. *J Nutr* 1993; 123: 346-50

5 Elder J. Kang S., Voorhees J. et al. Retinoid Induction of CRABP II mRNA in Human Dermal Fibroblasts. *J of Investigative Dermatology* 1996; 106: 517

6 Varani J. et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin. *J of Investigative Dermatology 2000*; 114: 480-86

7 Kang S, Fisher G. Voorhees J. et al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels of irritation. *J of Investigative Dermatology* 1995; 549-56

SUGGESTED READING:

Guttman C. Studies back retinol as photoaging tx. *Dermatology Times*

Vahlquist A., What are natural retinoids. *Dermatology 1999; 199 (suppl 1)3-11*

Griffiths CEM. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clinical and Experimental Dermatology* 2001; 26: 613-18