

The 21C Research Trend on the Cosmeceuticals

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Certain types of anti-inflammatory components and whitening components were in practical use as the active ingredients of quasi drugs expected to display their pharmacological actions. However, only twenty years at most have past since the introduction of cosmetics that not only physically change the condition of the surface of the skin, but also promote skin homeostasis from by acting on the physiological mechanisms of the skin. Since then, much effort has been made to find new active ingredients suitable for full-scale development, and the term “cosmeceutical” has often been coined to describe cosmetics containing pharmacologically active components. In this report, the prospects of cosmeceuticals will be discussed on the basis of a review of the history of the development of current skin-care products.

1. Significance of moisture retention in the horny layer

The horny layer of the skin must have an appropriate moisture content, both to fulfil its primary function as a barrier and to exhibit a subjectively beautiful appearance. The importance of NMF, mainly consisting of amino acids and their metabolites, in moisture retention and the importance of intercellular lipids in the barrier function have been recognized. In addition, there are findings indicating that NMF and intercellular lipids are closely associated with the keratinization process in the epidermis. On the other hand, studies on skin physiology focusing on dry skin have revealed that the occurrence of dryness or desquamation in dry skin is associated not only with a change in the horny layer, but also with a change in keratinization. This change in keratinization has been found to be the cause of a vicious cycle of changes in both the barrier function and the moisture retaining function. Thus, the importance of moisture retention in the horny layer in maintaining skin homeostasis has been re-affirmed. Through these studies, various non-invasive measuring methods have

been developed, and a quantitative skin physiology index for dry skin was established. Using these evaluation methods, the usefulness of skin-care cosmetics to improve dry skin was investigated. Skin-care preparations with an excellent moisturizing effect were found to restore the skin surface properties and the function of the horny layer, after 2 to 3 weeks of use, by promoting the normalization of keratinization. Before that, skin-care cosmetics were considered to act only physically to enhance moisture retention, but it is now clear that they also affect the physiological mechanisms of the skin.

2. Skin care focusing on enzyme reactions in the horny layer

Much is now known about the mechanisms responsible for the changes in symptoms of dryness and the changes in the barrier function which are characteristic of dry skin. However, the mechanism of the appearance of visible scales on dry skin was unknown for a long time. Recently we have clarified the mechanism of the normal desquamation of horny cells. That is, individual horny cells are peeled off from the surface of the skin, while the desmosomal protein, which is the main component of the connective structure, is gradually degraded by two types of proteases. These enzymes are activated in the final stage of the keratinization process. This degradation process is greatly affected by the water content of the horny layer, and a decrease in water content is, therefore, at least one factor responsible for the occurrence of abnormal desquamation in dry skin. Furthermore, it has been found that dicarboxylic acids possessing chelating action can normalize desquamation on the horny layer.

3. Skin care focusing on changes in epidermal function

Following the confirmation of the significance of moisture retention, studies have been conducted to examine the pharmacological effects of various compounds in terms of normalization of abnormal proliferation of cells in the epidermis and the metabolic changes in dry skin. The pathophysiological mechanisms responsible for the occurrence of dry skin were studied by means of pharmacological approach. In an experimental model of dry skin with abnormal proliferation of cells in the epidermis, the effects of various known drug products were investigated. The study demonstrated that plasminogen activation system are closely involved in the occurrence of dry skin, and activation of this system triggers changes

in proliferation and differentiation of epidermal keratinocytes. We have found that the anti-plasmin agent 4-aminomethylcyclohexanecarboxylic acid suppresses these changes. This compound showed excellent effectiveness in improving dry skin, not only in an experimental model of dry skin, but also in human dry skin during winter. Based on this study, approval of this compound as an active ingredient in medicated cosmetics has been obtained from the Ministry of Health and Welfare of Japan. The value of simple moisturizing preparations for dry skin remains clear. However, the development of active ingredients which can act directly on the control mechanisms specific to epidermal proliferation and differentiation should allow the development of far more effective products.

4. Skin care focusing on the epidermal-dermal interaction

At present, the major sites of action of skin-care cosmetics are the horny layer and the epidermis. However, it has become clear that the homeostasis of the epidermis is maintained by the dermis located directly underneath it, and that the structure and function of the dermis are in turn affected by the epidermis. This epidermal-dermal interaction is controlled by the basement membrane between them, which has a thickness of only 0.1 microns. The basement membrane itself is formed through the cooperative activity of epidermal keratinocytes and dermal fibroblasts. Recent studies have revealed that structural abnormalities, such as multiplexing and laceration, in the basement membrane of the sun-exposed skin, such as the facial skin, start to occur even in people in their late twenties. We consider changes in the structure of the basement membrane to be an early sign of skin aging. This is because destruction of the basement membrane causes not only abnormal proliferation and differentiation of keratinocytes, but also induction of matrix-degrading enzymes (matrix metallo-proteinases: MMPs) in the epidermis. Studies in experimental models of photoaging have demonstrated that the repair of the basement membrane is promoted by compounds that stimulate the synthesis of laminin 5, a basement membrane component that directly binds to a receptor on the membrane of keratinocytes. Furthermore, MMP inhibitors suppress various symptoms of photoaging, including wrinkle formation and UV-induced destruction of the basement membrane.

5. Skin care focusing on the connection between the mind and the skin

Local processes in the skin are not the only factors involved in the homeostasis of the skin. It has been known for a long time that the condition of the mind can influence the physiological function of the skin. It has been demonstrated recently that psychological stress has an impact on the autonomic nervous system, the endocrine system and the immune system, which secondarily influence the skin and other organs.

The effects of stress include the following: alterations in lipid synthesis in the sebaceous glands; reduced proliferation of epidermal keratinocytes and thinning of the epidermis; delay in repair of the barrier function of the horny layer; enhance pigmentation upon exposure to UV rays. Stress has a significant impact on the immune system, inducing morphological and functional changes in Langerhans cells which lead to suppression of contact hypersensitivity reactions. These changes in the skin are caused by stress-induced enhancement of the functions of the hypothalamus-pituitary-adrenal system. Interestingly, some fragrance compounds can reducing the effects of stress. Recent studies has demonstrated that a sedative component of rose oil, 1,3-dimethyl-5-methylbenzene is effective to prevent the decrease of the capacity for restoration of the barrier function of the skin by stress in humans.

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In this paper, I have briefly discussed the history of skin-care cosmetics that act on the physiological mechanisms of the skin, citing some of the research conducted in our company. The purpose of skin care is, needless to say, to prevent, delay or reverse changes in the skin that are unfavorable in terms of health or beauty, by the use of component with mild actions. The range of changes in the skin that may be targeted by cosmeceuticals has become increasingly diverse. The ultimate objective is to contribute to the attainment of a higher quality of life in our progressively aging society, by minimizing skin changes that appear with aging. As presented in this article, the site of action of the base or active ingredient of skin-care cosmetics has been extended from the horny layer to the epidermis, basement membrane and dermis, and at present is being further extended to the regulatory system throughout the whole body, as our understanding of the physiological mechanisms of the skin deepens. The twenty-first century is likely to see real achievements in the development of cosmeceuticals that have mild but wide-ranging effects in normalizing various functions of human body.