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Improvement Effect of Magnesium on Aging-Induced Decrease in Ceramide Production in the Skin

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Summary

Over 70% of elderly people may have skin problems, and the patients with skin diseases will increase in the future. The epidermis of the skin is made up of four layers: stratum corneum, stratum granulosum, stratum spinosum, and stratum basale, and functions as a barrier to prevent the invasion of foreign substances from the outside and the evaporation of water from within the body. Moisturizing factors such as ceramide and collagen in the stratum corneum, and intercellular tight junctions in the granular layer play important roles in forming the barrier function. The barrier function is reduced by aging and exposure to ultra violet rays and oxidative stress. Therefore, factors that enhance the production of moisturizing factors can be expected to enhance the skin barrier function in elderly people. In addition, repair mechanisms for physical wounds also play an important role in maintaining skin barrier function. Magnesium has been reported to have a promoting effect on skin wound healing, but the detailed mechanism remains unclear. In this study, we investigated the effect of magnesium on ceramide production and wound healing. Furthermore, we searched for food materials that can improve the aging-induced barrier dysfunction.

HaCaT cells and NHEK cells derived from human epidermal keratinocytes were used in the experiment. The gene and protein expression were analyzed by real-time PCR and Western blotting, respectively. Intracellular free magnesium concentration ($[Mg^{2+}]_i$) was measured using the fluorescent indicator, mag-fura 2. The transcriptional activity of (*NIPA like protein 4*) *NIPAL4*, a magnesium channel coding gene, was measured using luciferase assay. In the wound healing assay, the area of the wound caused by the pipette tip was measured and the closure rate was compared.

Tenovin-1, a sirtuin inhibitor, increased the amount of acetylation of p53, an aging factor, and decreased the amount of *NIPAL4* mRNA. The resting level of $[Mg^{2+}]_i$ was decreased by tenovin-1 and knockdown of *NIPAL4* using siRNA. These results suggest that tenovin-1 decreases the resting level of $[Mg^{2+}]_i$ mediated via the reduction of NIPAL4 expression. The expression levels of enzymes involved in the production of sphingomyelin, which is a material for ceramide synthesis, were decreased by tenovin-1. Using a compound library, we searched for food materials which activate a transcriptional activity of NIPAL4 and identified resveratrol. Resveratrol improved the decrease in ceramide synthase expression and sphingomyelin concentration caused by tenovin-1. Next, we investigated the role of magnesium on wound healing and found that it increases the expression of matrix metalloproteinases 7 (MMP7), which enhances cell migration. The increase in MMP7 expression was inhibited by U0126, a MEK/ERK pathway inhibitor, suggesting the involvement of this signal transduction pathway.

In conclusion, we suggest that magnesium deficiency is involved in the aging-induced dysfunction of skin barrier. Resveratrol improved the tenovin-1-induced reduction of *NIPAL4* expression and paracellular barrier. Resveratrol may be a candidate for an antiaging food material.