Orally Applied Novel Organogermanium Improves Skin Inflammation in NC/Nga Mice with Atopic Dermatitis

Soyeong Kang, Yeoju Moon, Taeho Ji, Siyoung Ha, Doo Hyeon Lim, and Seung Wook Ham*

Department of Chemistry, College of Natural Science, Chung-Ang University, Seoul 156-756, Korea. *E-mail: swham@cau.ac.kr

Received August 13, 2012, Accepted October 4, 2012

Key Words : Organogermanium, Atopic dermatitis (AD), Murine model, anti-AD activities

It has been reported that compounds containing germanium (Ge) have a broad range of biological activities. In general, inorganic forms of germanium are severely toxic to certain organs and tissues, whereas organic forms of germanium compounds appear to be less toxic for mammals. Therefore, many organogermanium compounds have been synthesized and investigated for their pharmacological activities. However, in spite of its beneficial effects, long-term ingestion or exposure to germanium could cause severe acute and chronic health effects in humans. Therefore, it is necessary to develop compounds that have fewer side effects than inorganic forms of germanium. The organogermanium as along with improved water solubility would be improved by the combined effects of ascorbic acid and organogermaium because the antioxidant activity of this conjugated compound (Ge-Vit) might be improved with the ointment base-treated group, as shown in Figure 1(b). Histological examination further supported the anti-inflammatory effects of this compound on atopic dermatitis (AD) were investigated because atopic dermatitis is a type of chronic inflammatory disease of the skin. It has been reported that the Dermatophagoides farinae (Df) extract ointment-induced dermatitis model in NC/Nga mice is useful for elucidating the pathogenesis of atopic dermatitis and for evaluating therapeutic agents. Therefore, in this study, induction of AD using Df body ointment was performed as described previously. Briefly, on day 0, mice were treated with 150 μL of 4% sodium dodecyl sulfate after shaving the hair on the backs of pathogen-free male NC/Nga mice (aged 7-8 weeks, 20-25 g). Df body ointment (150 mg per mouse) was then applied to the dorsal skin and both ears of each ear 6 times over the course of 3 weeks to induce AD-like skin lesions. Ascorbyl 2-palmitate, which is one of lipophilic and stable 2-O-substituted ascorbate derivatives, showed vitamin C activity after enzymatic hydrolysis to free vitamin C by a certain esterase in vivo. Therefore, the compound dissolved in PBS was administered orally once a day for 3 weeks. Prednisolone (10 mL/kg) and PBS alone were used as positive control and vehicle control, respectively, over the same treatment period.

Clinical symptoms of AD were assessed according to four symptoms: erythema/hemorrhage, scarring/dryness, edema and excoriation/erosion. In order to evaluate the effects of the compound on skin barrier function, the basal TEWL (Transepidermal Water Loss) values of the back and both ears of the mice were measured first at the end of the treatment period. The TEWL values of the mice treated with compound 1 and prednisolone decreased (51% at compound 10pmk, and 48% at prednisolone 3pmk) compared to the vehicle-treated group, indicating that treatment of compound 1 affected the basal TEWL. In addition, in the clinical skin score which was determined macroscopically from the sum of individual scores according to four AD symptoms, treatment of compound 1 was shown to significantly improve the dermatitis score in the compound-treated NC/Nga mice compared with the ointment base-treated group, as shown in Figure 1(b). Histological examination further supported the anti-AD activities of this compound, and both dermal inflammation and parakeratosis were substantially alleviated (Figure 1(d)) along with attenuation of inflammatory cell infiltration. Allergen-specific CD4+ T cells can be isolated from the skin lesions of patients with AD. On the basis of their cytokine production profiles, CD4+ helper T lymphocytes were subdivided into type 1 T-helper (Th1) and type 2 T-helper (Th2) cells, and the predominance of Th2 and increased serum IgE levels were reported in patients with atopic dermatitis. However, in the present study, the level of IgE in the compound-treated group still remained high, while predominant expression of IgE was observed in the Df extract ointment.
induced dermatitis model and a lower IgE production level was exhibited in the prednisolone-treated mice than the control group (Figure 1(c)). Previously, we reported that a novel water-soluble organogermanium compound (Ge-OH) conjugated with glucose enhance INF-γ, resulting in the anti-inflammatory effect. Meanwhile, oral administration of high dosages of vitamin C to the mice increased the secretion ratio of Th1/Th2 (INF-γ/IL-5) cytokines in the bronchoalveolar lavage fluid (BALF), suggesting that a high dose of the vitamin C supplement might attenuate allergic inflammation in vivo by modulating the Th1/Th2 balance toward the Th1 pole. Although down-regulation of IgE was not detectable within 3 week, the prolonged treatment of compound might result in the dereased level of IgE through INF-γ production. These suggest that the expression of other Th1 and Th2 cytokines needs to be clarified in detail in order to determine the molecular mechanisms of the immune-modulating effects between IgE/INF-γ.

Although steroids have widely been prescribed for patients with AD, skin abnormalities, such as skin atrophy and epidermal barrier disturbance, are frequently observed after prolonged steroid treatment. Regarding the side effects, our study results suggest that compound 1 can be a useful drug candidate for the treatment of atopic dermatitis.

**Acknowledgments.** This research was supported by the Chung-Ang University Research Scholarship Grants in 2012.

**References and Notes**


