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# Water-retaining function in the stratum corneum and its recovery properties by synthetic pseudoceramides

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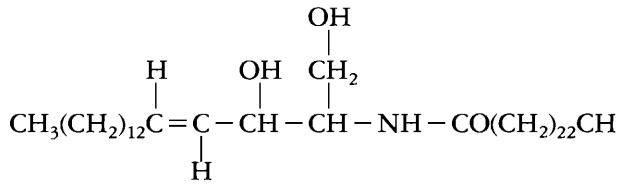
**Synopsis**

We have recently found that lipids that form lamellar structures in the intercellular spaces of the stratum corneum can be specific modulators for water-retaining properties of the stratum corneum. Among the intercellular lipids, ceramide (A) fractions exhibit the highest capacity for recovering diminished water-retaining properties. In order to clarify the role of ceramides in the water-retaining function of the stratum corneum, we have synthesized pseudoceramide (B) derivatives and examined their potential for repairing the lipid-depleted stratum corneum, in which a marked decrease in the water-retaining properties is found. Synthesized pseudoceramide derivatives are characterized by structures having both amide or nitrogen bonds and hydroxyl groups as hydrophilic units, as well as two long alkyl chains. When the polar group has an amide bond in the main linkage with hydroxyl ether binding at nitrogen atom, topical applications of these compounds (solubilized at 1–3% in squalane or W/O cream) to acetone/ether or sodium dodecyl sulfate-induced dry skin showed a significant recovery of water-retaining properties—accompanied by an improvement in scaling—over that induced by base cream. Analysis of alkyl chain properties has revealed that a structural requirement for the recovery of the water-retaining capacity is the presence of saturated-straight alkyl chains whose structural characteristics are very similar to naturally occurring ceramide in the stratum corneum and the absence of unsaturation or methyl branching. However, the observed alkyl chain length (14–18 carbons) preferred for water-retaining function is different from that of the major naturally occurring ceramides, indicating differential contributions of ceramide structures to stratum corneum functions. The present evidence suggests that ceramides with relatively shorter alkyl chain lengths serve as water modulators in the multilipid bilayers within the stratum corneum.




(A)

Ceramide
N-Acyl Sphingosine



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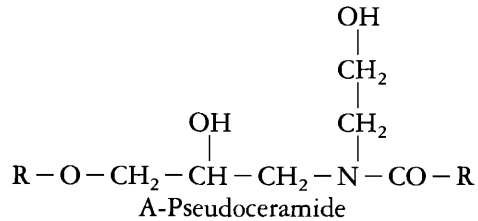


(B)

## INTRODUCTION

We have recently found that lipids that form lamellar structures in the intercellular spaces of the stratum corneum can be specific modulators for water-retaining properties of the stratum corneum, whose function is reversible by topical applications of the intercellular lipids (1,2). Among the intercellular lipids, the ceramide fraction is found to possess the highest capacity for repairing diminished water-retaining properties (3). Ceramides are unique heterogeneous materials capable of forming multilamellar structures in the absence of phospholipids. This lamellar-forming ability is suggested to be involved with the water-retaining properties (3,4), as was previously elucidated for the water barrier function of the stratum corneum (5). Although several species of ceramides have been identified from the intercellular lipids of the stratum corneum (6), little is known about the precise potential for their proposed functions because of limited availability of natural ceramides for experimentation. Lipid-depleted stratum corneum following acetone/ether (3) or sodium dodecyl sulfate treatments (7) was found to be useful as a model for a deficiency in the amount of ceramides that is directly involved in the induction of dry skin, because ceramides are major and essential components of stratum corneum lipids. In order to clarify the role of ceramides in the water-retaining function of the stratum corneum and the structural characteristics responsible for maintaining water, we have synthesized pseudoceramide derivatives and examined their repair potential on the lipid-depleted stratum corneum, in which a marked decrease in the water-retaining properties is found. In this paper, we report structural features of ceramides relevant to the water-retaining function.

## MATERIALS AND METHODS

### MATERIALS

Amide derivatives were principally synthesized by the following stepwise process: Glycidylether was first produced by reaction of the appropriate alcohol, epichlorohydrin, and 50% aqueous tetrabutylammonium bromide in hexane with 50% aqueous sodium hydroxide at 50–55°C. The appropriate glycidylether was then added dropwise under heating at 60–70°C to the ethanolamide and ethanol, to yield an ethanolamide adduct (B) after purification by flash chromatography. In some cases, the ethanolamide adduct was stirred with methylcarboxylate and powdered potassium hydroxide under reduced pressure at 80–100°C to yield other amide derivatives that were double recrystallization from ethanol. The synthesized amide derivatives are as follows:

{*1*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-2-hydroxyethylhexadecanamide, {*2*}:

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N,N-bis(3-hexadecyloxy-2-hydroxypropyl)-2-aminoethanol, {*3*}: Sodium N,N-bis(3-hexadecyloxy-2-hydroxypropyl)glycinate, {*4*}: N,N-bis(3-hexadecyloxy-2-hydroxypropyl)glycinate, {*5*}: N,N-bis(3-hexadecyloxy-2-hydroxypropyl)acetamide, {*6*}: 3,4-di-O-(z)-9-octadecenoyl-D-mannitol, {*7*}: N-hexadecylhexadecanamide, {*8*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-methylhexadecanamide, {*9*}: N-2-hydroxyeicosyl-N-2-hydroxyethylhexadecanamide, {*10*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-3-hydroxypropylhexadecanamide, {*11*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-6-hydroxyhexylhexadecanamide, {*12*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-2-(2-hydroxyethoxy)ethylhexadecanamide, {*13*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-2,3-dihydroxypropylhexadecanamide, {*14*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyloxylpropyl)octadecanamide, {*15*}: N-(3-dodecyloxyl-2-hydroxypropyl)-N-2-hydroxyethyloctadecanamide, {*16*}: N-(3-hexadecyloxyl-2-hydroxypropyl)-N-2-hydroxyethyloctadecanamide, {*17*}: N-2-hydroxyethyl-N-(2-hydroxy-3-octadecyloxylpropyl)octadecanamide, {*18*}: N-2-hydroxyethyl-N-(2-hydroxy-3-octadecyloxypropyl)decanamide, {*19*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyloxypropyl)dodecanamide, {*20*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-2-hydroxyethyldodecanamide, {*21*}: N-2-hydroxyethyl-N-(2-hydroxy-3-octadecyloxypropyl)dodecanamide, {*22*}: N-2-hydroxyethyl-N-(2-hydroxy-3-octadecyloxypropyl)hexadecanamide, {*23*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-2-hydroxyethyltetradecanamide, {*24*}: N-(3-docosyloxy-2-hydroxypropyl)-N-2-hydroxyethyldecanamide, {*25*}: N-(3-decyloxy-2-hydroxypropyl)-N-hydroxyethyldecanamide, {*26*}: N-(3-decyloxyl-2-hydroxypropyl)-N-2-hydroxyethyloctadecanamide, {*27*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyloxypropyl)tetradecanamide, {*28*}: N-(3-hexadecyloxy-2-hydroxypropyl)-N-2-hydroxyethyl-methylheptadecanamide, {*29*}: N-2-hydroxyethyl-N-(2-hydroxyl-3-methylheptadecyloxypropyl)methylheptadecanamide, {*30*}: N-2-hydroxyethyl-N-(2-hydroxy-3-methylheptadecyloxypropyl)hexadecanamide, {*31*}: N-(3-decyloxyl-2-hydroxypropyl)-N-2-hydroxyethyldocosanamide, {*32*}: N-2-hydroxyethyl-N-(2-hydroxy-3-octadecyloxypropyl)tetradecanamide, {*33*}: N-(3-dodecyloxy-2-hydroxypropyl)-N-2-hydroxyethyl-(z)-9-octadecenamide, {*34*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyloxylpropyl)hexadecanamide, {*35*}: N-(3-dodecyloxy-2-hydroxypropyl)-N-2-hydroxyethylhexadecanamide, {*36*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyloxypropyl)decanamide, {*37*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyloxylpropyl)docosanamide, {*38*}: N-2-hydroxyethyl-N-(2-hydroxy-3-tetradecyl(oxypropyl)-(z)-9-octadecenamide.

Petrolatum, squalene, octyl-dodecyl myristate, cholesterol, cholesterol ester, and stearic acid were obtained from Wako Chemical (Tokyo, Japan). Naturally occurring ceramide was purchased from Sigma Chemical Co. (Saint Louis, MO).

### TREATMENT WITH ACETONE/ETHER OR SODIUM DODECYL SULFATE

The forearms of 7–13 healthy volunteers, aged 24–33 years, were used for each experiment. Open-end, 3-cm-diameter cylinders filled with 10 ml of acetone/ether (1/1) or sodium dodecyl sulfate (SDS) at 5% concentration were gently pressed with occasional shaking onto the sample areas for 30-min periods to induce dry skin (day −1). They induced a chapped and scaly appearance of the stratum corneum that persisted until at least day 4 after treatment (2).

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### APPLICATION OF COMPOUNDS

Synthetic compounds were solubilized at 1–5% concentrations in squalene containing 1% α-monomethyl heptadecyl glyceryl ether (GE, Kao Corp, Tokyo, Japan) or W/O cream consisting of 2% GE, 3% petrolatum, 5% squalane, and 10% octyl-dodecyl myristate. This cream was applied daily at 0.014 ml/area (approximately 2 $\mu l/cm^2$) from the first day (day 0) after 30 min acetone/ether or SDS treatment for 2–3 successive days, or once one hour after 30-min acetone/ether treatment.

### MEASUREMENT OF WATER-RETAINING CAPACITY OF THE STRATUM CORNEUM

Water-retaining capacity of the stratum corneum was measured according to the method of Tagami *et al.* (8). Changes in water content of the treated areas were measured by a capacitance conductance meter (model IB-354, IBS Inc., Japan). Treated areas were rinsed with water at 37°C and then, after keeping volunteers at 20°C and 50% humidity for 20 min, were measured for skin reaction and conductance value 24 hours (day 3) or four hours after the last sample application, or daily through the period of experiment. Conductance measurements were carried out five times at the same area, and the values were averaged to obtain individual values.

### MEASUREMENT OF SKIN REACTION

The skin reaction, including scaling, was observed three days (day 3) after acetone/ether treatment under the same conditions as conductance measurement. Scaling was assessed according to the following scale: no scaling = 0, slight scaling = 1, moderate scaling = 2, marked scaling = 3.

### STATISTICS

The level of significance of the difference was calculated by Student's t-test for paired comparison for conductance values and by Friedman's test for scaling.

## RESULTS

Topical applications to acetone/ether-induced dry skin of the synthetic pseudoceramides that have different polar groups but the same alkyl chain length with an ether bond, emulsified at 1% in a W/O cream, showed a significant recovery of the decreased conductance value, as compared with nontreatment control or base cream when the polar group has an amide bond, while the application of base cream only failed to produce any significant recovery (Figure 1). The applications of naturally occurring ceramide from calf brain (NOC) also showed a significant recovery as compared with the nontreatment control (Figure 2). Among three different structures with amide bonds in the main linkage, a structure with two hydroxyl groups {*1*} is found to exhibit the highest potential to improve water-retaining properties, accompanied by a significant improvement of scaling induced by acetone/ether treatment (Figure 3). Comparing compound {*9*} with compound {*1*} in Figure 4, it is clear that the substitution of a carbon–carbon bond for the ether bond found near the polar end of alkyl chain provides a less efficient recovery effect. This suggests that the ether bond in this structure (B) is similar to a

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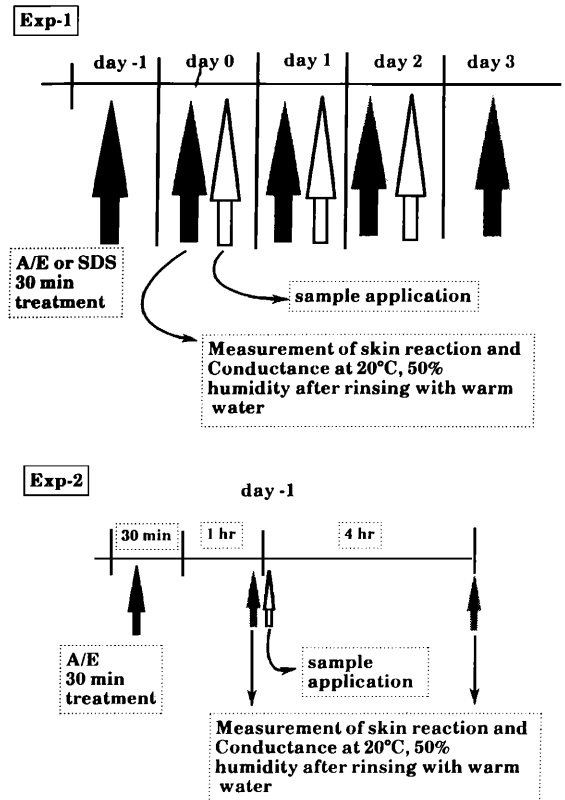


**Figure 1.** Procedures of sample applications and measurements. All experiments were carried out in either Exp-1 or Exp-2. A/E: acetone/ether (1/1). SDS: sodium dodecyl sulfate (5% aqueous solution).

double bond in ceramide (A) and helps to promote water-retaining capacity. With respect to the properties of attached hydroxyl groups, a structure with hydroxyethyl group at the amide residue {*1*} is found to be most suitable for acquiring the water-retaining properties in comparison to structures with hydroxypropyl {*10*}, hydroxyhexyl {*11*}, hydroxyethyoxy ethyl {*12*}, and dihydroxy propyl {*13*} groups (Figure 4).

Since a structure consisting of a polar amide bond and hydroxyethyl groups in a structure like {*2*} is found to have potential for repairing the water-retaining function and is apparently a good substitute for naturally occurring ceramides, this basic pseudoceramide frame in the polar tail allows for the subsequent quantitation of the influence by alkyl chain properties that are an essential part of the biologic function of the stratum corneum lipids. Structures such as those with double bonding {*33, 38*} and methyl branching {*28, 29, 30*} provide a markedly negative influence on the recovery potential (Figures 5, 6), indicating that one of the structural requirements for the water-retaining function is the presence of two saturated alkyl chains. Analysis of saturated alkyl chain length shows a structure 31 carbons long in total {*1, 14*} to be the best suited for the water-retaining properties (Figures 5, 6). In order to clarify the time course and dose dependency of the recovery in the conductance values, the best suited pseudoceramide {*1*} at 3 and 5% concentrations was applied daily for three successive days (from day 0 to

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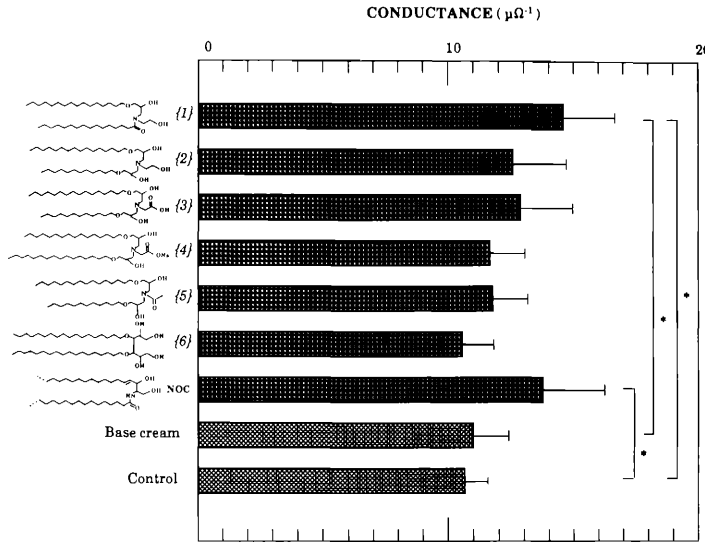


**Figure 2.** The repair effect of synthetic pseudoceramide with different polar groups on acetone/ether-induced dry skin as measured by conductance value. One day (day 0) following acetone/ether treatment (day −1), each pseudoceramide emulsified in W/O cream at 1% concentration was applied daily for two days and conductance was measured 24 hours (day 3) after the last application of samples (day 2) according to procedure Exp-1. Bar represents standard error. *$p < 0.05$, between samples and base cream or non-treated control. $n = 13$. NOC: naturally occurring ceramide from calf brain.

day 2) and its effect evaluated daily. A significant increase relative to the base cream was observed with 3 and 5% pseudoceramide within two days after the first application, with the 5% application showing a higher recovery than the 3% (Figure 7). The best compound {*1*} was also found to exhibit a similar significant recovery effect on SDS-induced dry skin, as revealed by an increased conductance value and improved scaling (Figure 8).

## DISCUSSION

Our previous lipid-depletion and replenishment experiments have revealed that sphingolipids, especially ceramides, play an essential role in the establishment or maintenance of the water-retaining properties in the stratum corneum, whose impairment could be a consistent accompaniment to pathologic dry skin (2,3). It has recently been demonstrated (9) that ceramides from pig stratum corneum are separated into six distinguishable fractions. The major ceramide (42.4%) contains saturated nonhydroxy fatty acids ranging from 14 through 33 carbon atoms, bound in amide linkage to sphingosine and dihydrosphigosines ranging from 16 through 22 carbons in length. Along with ordinary ceramides, recently unique ceramides with ω-hydroxyacids, esterified with fatty acids, predominantly linoleic, have been isolated from human stratum corneum (6,9). These ceramides have been implicated as important to the barrier function or the cohesion-abhesion of the stratum corneum. Although these results have been substan-

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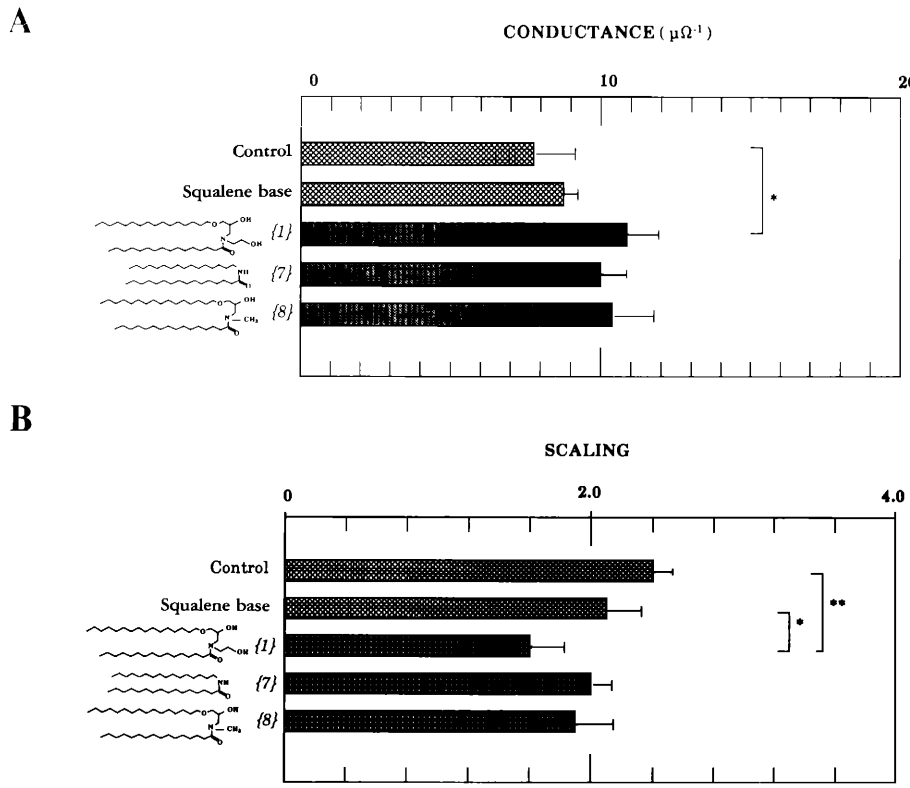


**Figure 3.** The recovery effect of synthetic pseudoceramides with amide group on acetone/ether-induced dry skin. One day following acetone/ether treatment, each pseudoceramide solubilized in squalene containing 1% GE at 1% concentration was applied daily for two days according to procedure Exp-1. Bar represents standard error. *$p < 0.05$. **$p < 0.01$, between samples and squalene base or nontreated control. $n = 10$. A: Evaluation by conductance measurement. Conductance was measured 24 hours (day 3) after the last application of samples (day 2). B: Evaluation by skin reaction. Scaling was evaluated 24 hours (day 3) after the last application of samples (day 2) according to the criteria described in Materials and Methods.

tiated by comparison of the lipids on the basis of their altered proportions relative to the normal situation, further work is needed to evaluate the potential of these lipids for their role in the stratum corneum functions and to clarify how individual structures of the ceramides contribute to their functions.

Water-retaining properties of the stratum corneum have been implicated as a different function from the water permeability barrier, although the interrelationship between the water barrier and water-retaining functions has been suggested in pathologic stratum corneum but not in normal skin (10). In fact, acetone/ether-induced scaly dry skins, which have markedly defective water-retaining properties, do not necessarily exhibit a significantly increased transepidermal water loss (TEWL), probably because of superficial alteration of the stratum corneum (1). The presence of lipid bilayers between the stratum corneum cells is in itself sufficient to account for the water-retaining capacity of the stratum corneum, because water molecules are strictly compartmentalized

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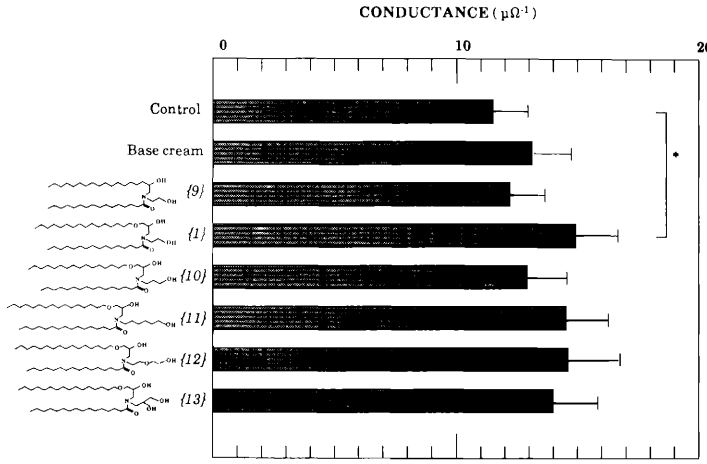


**Figure 4.** Comparison of the recovery of conductance value between synthetic pseudoceramide with different hydroxyl groups and the effect of substitution of carbon bond for an ether bond in alkyl chain on the recovery of conductance value. One hour following acetone/ether treatment, each pseudoceramide solubilized at 1% concentration in base cream was applied once, and conductance was measured four hours after the application of samples according to procedure Exp-2. Bar represents standard error. $*p < 0.05$, between samples and nontreated control. $n = 8$.

as a structural unit in the intercellular lipid bilayers. In contrast, the expression of the water barrier function should require an additional complicated arrangement of lipids different from typical biologic bilayers because of the free passage of water through these lipids. Synthetic pseudoceramide is a very useful tool for elucidating the molecular and physical structures of importance to the water-retaining function of the stratum corneum, because these properties have been found to be partially reversible by the addition of specific pseudoceramide structures (3). In the present study the synthetic compounds that provided a significant recovery potential for diminished water-retaining properties of the stratum corneum are structures having both an amide group that serves as a link between two long hydrocarbon chains and free hydroxyl groups attached near the nitrogen atom. It has been suggested that the amide group has a basic significance for the conformation of the entire molecule to adopt a perpendicular orientation towards the axes of the two hydrocarbon chains (11), which facilitates the formation of lipid bilayers in combination with other neutral lipids. Besides the amide group, hydroxyl groups allow the formation of lateral hydrogen bonds that may be essential for holding water molecules within the membrane layers (11). Thus, the observed structural characteristics are in accord with the essential role of ceramides proposed for water-retaining properties of the stratum corneum. Since there are many structural variations, especially in the length of hydrocarbon chains in the hydrophobic tails of

**Figure 5.** Comparison of the recovery of conductance value among synthetic pseudoceramides with different alkyl chains properties. One day (day 0) following acetone/ether treatment (day −1), each pseudoceramide solubilized at 1% concentration in squalene containing 1% GE was applied daily for two days, and conductance was measured 24 hours (day 3) after the last application of samples (day 2) according to procedure Exp-1. Bar represents standard error. $*p < 0.05$, between samples and squalene base or nontreated control. A-1: $n = 9$. A-2: $n = 10$. B-1: $n = 7$. B-2: $n = 8$.

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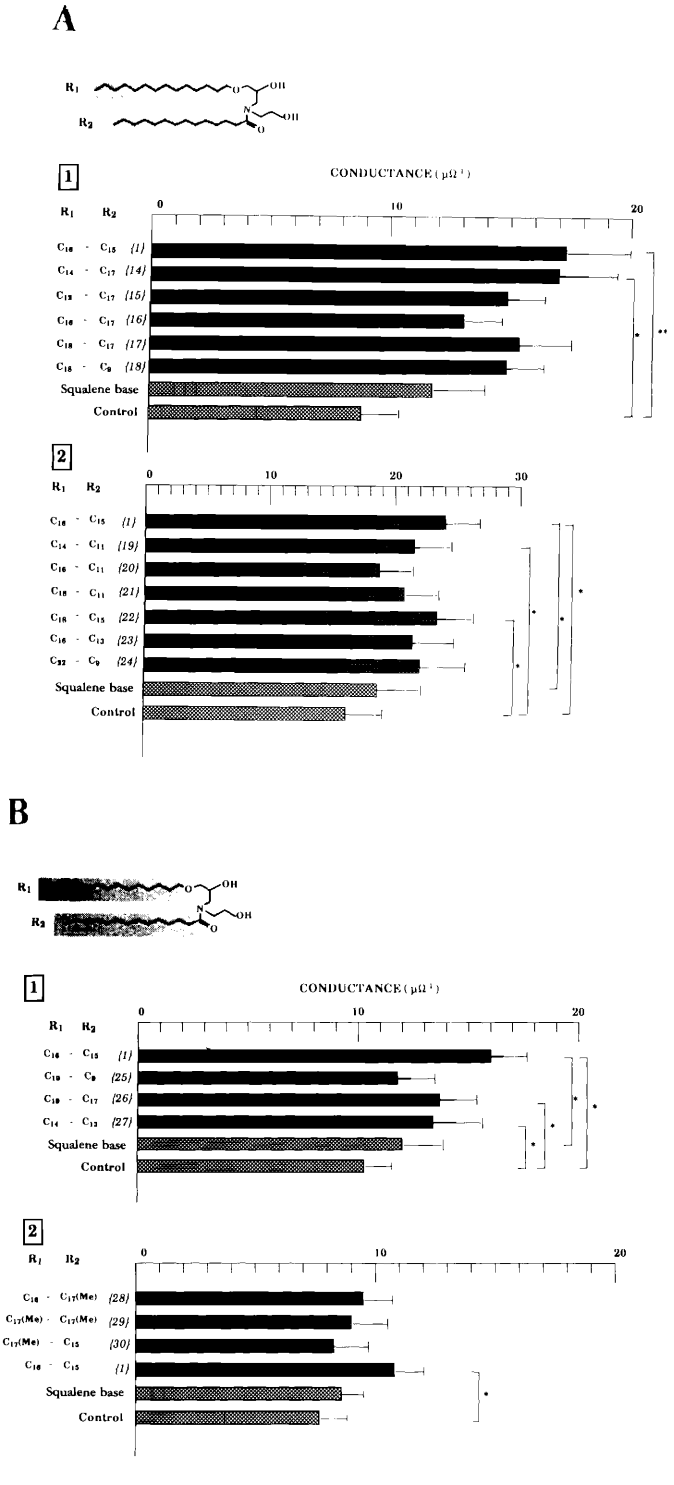


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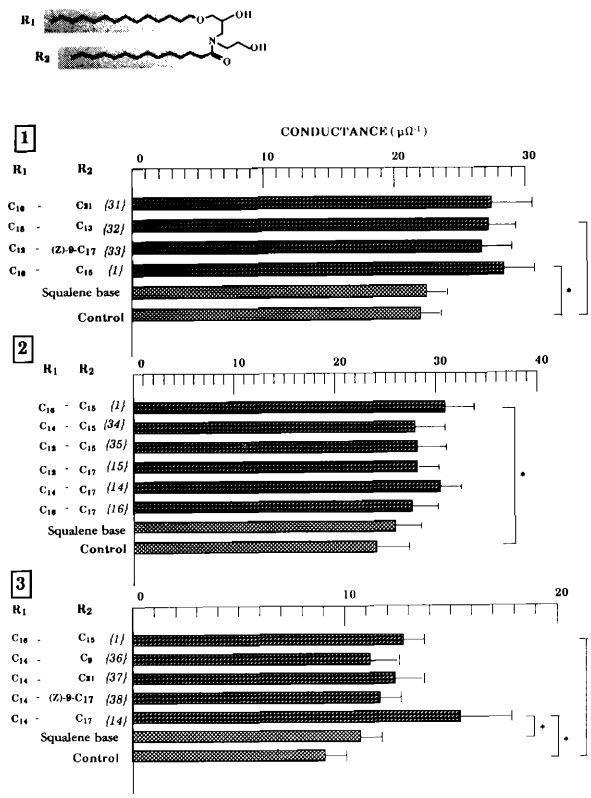


**Figure 6.** Comparison of the recovery of conductance value between synthetic pseudoceramide with different properties of alkyl chains. One hour following acetone/ether treatment, each pseudoceramide solubilized at 1% concentration in squalene containing 1% GE was applied once, and conductance was measured 4 hours after the application of samples according to procedure Exp-2. Bar represents standard error. $*p < 0.05$ between samples and squalene base or nontreated control. 1: n = 8. 2: n = 7. 3: n = 10.

ceramides, it is of interest to know whether functional differences are dependent on variations in chain length. With respect to the properties of hydrocarbon chains, the incorporation of a double bond or methyl branch into the hydrocarbon chain is found to impair the water-retaining function. The optimum structural requirement for serving the water-retaining function was the presence of two saturated hydrocarbon chains with a total of 31 carbon numbers. These characteristics are in good agreement with the fact that the hydrophobic chains observed in ceramides of human stratum corneum are predominantly straight and saturated. However, the observed alkyl chain length preferred for the water-retaining function is quite different from that of the major naturally occurring ceramides, which contain mainly 18–20 carbon sphingosines and amide-linked nonhydroxyacids 24–26 carbons in length (9), resulting in a total length of more than 40 carbons. It seems reasonable to assume that the high degree of chain length variation among the stratum corneum ceramides may also be significant, with each contributing to different stratum corneum functions such as water-retaining properties, cohesion, and the water permeability barrier function. For instance, O-acylcera-

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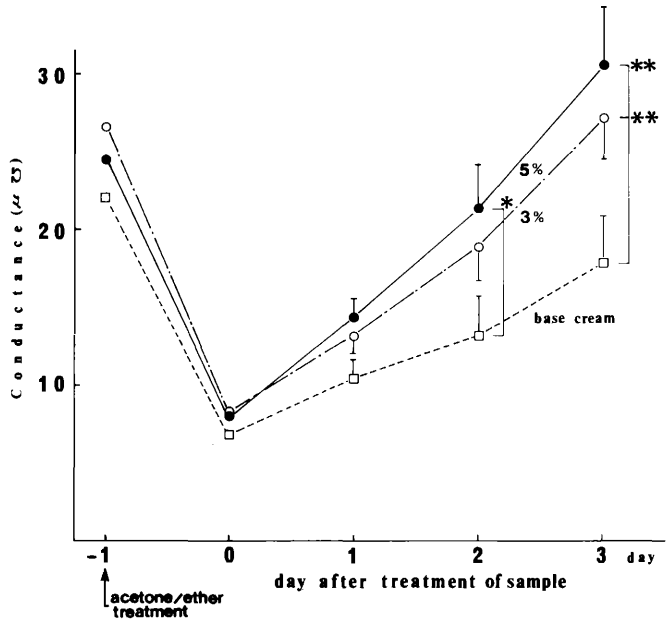


Figure 7. The time course and dose dependency of the recovery effect by the best suited ceramide {*1*}. The forearm skin of healthy male volunteers was treated with acetone/ether for 30 minutes (day −1). The sample emulsified in W/O base cream at the indicated concentrations was applied daily from day 0 to day 2 according to Exp-1 procedure. Conductance value was measured daily in comparison with base only. *$p < 0.05$. **$p < 0.01$. $n = 10$.

mides, which contain an amide-linked long chain ω-hydroxy acid and linoleic acid esterified to the ω-hydroxyl group, are thought to play an important role in maintaining the multi-bilayer organization of the barrier lipids (9).

It has recently been documented that the presence of amphipathic lipids such as ceramides are required for the lipid bilayers between stratum corneum cells to be constructed because the stratum corneum is virtually void of phospholipids (12). In this connection, preparation of liposomes from stratum corneum lipids has been documented (13, 14). Since our previous optical microscope analysis of synthetic psuedoceramides in a mixture with other neutral lipids of stratum corneum suggested that the capacity to form multiconcentric lamellae vesicles *in vitro* is the minimum requirement for the water-retaining function (4), this may account for the necessity for the observed distinct balance of chain length between two hydrophobic domains of pseudoceramides in exerting the water-retaining function of the stratum corneum.

Of considerable importance is the fact that topical applications of pseudoceramides also provide significant improvement of scaly, dry skin, which is accompanied by recovery in the water content of the stratum corneum. Since it has recently become evident that there is a deficiency in the amount of ceramide or an abnormality in the distribution or structures of the ceramides in skin diseases (6, 15, 16), the newly synthesized pseudoceramides can be a useful tool for improving dry skin conditions as well as for clarifying the mechanisms underlying dry skin.

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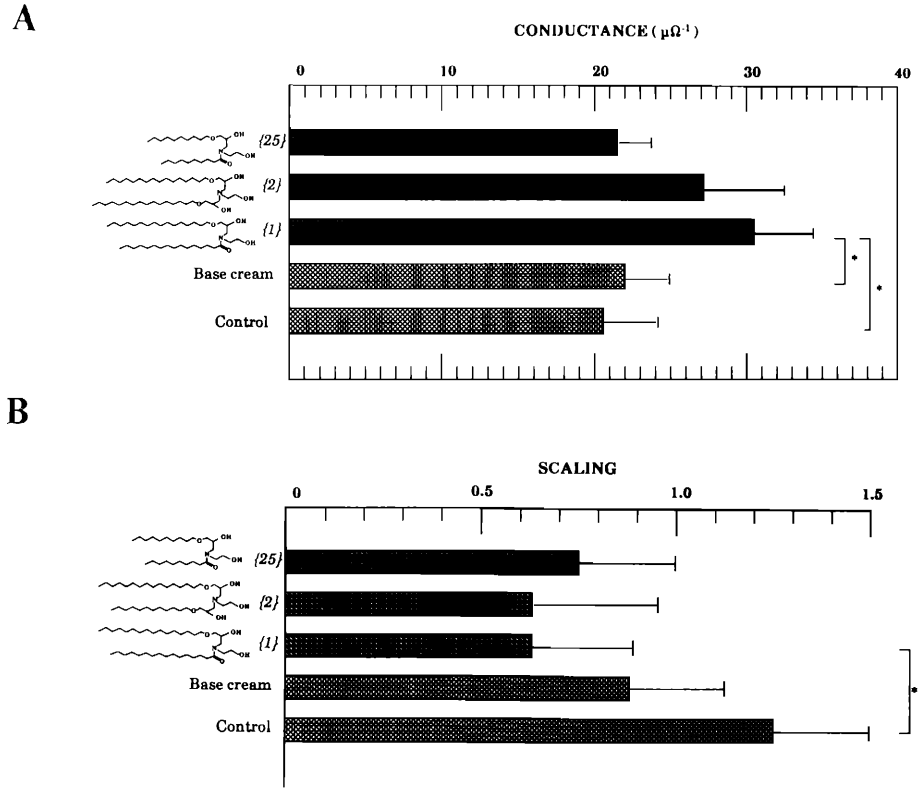


**Figure 8.** The recovery effect of synthetic pseudoceramides on SDS-induced dry skin. One day (day 0) following 5% SDS treatment (day −1), each pseudoceramide emulsified in W/O cream at 3% concentration was applied daily for two days according to procedure Exp-1. Bar represents standard error. *$p < 0.05$ between samples and base cream or non-treated control. $n = 7$. A: Evaluation by conductance measurement. Conductance was measured 24 hours (day 3) after the last application of samples (day 2). B: Evaluation by skin reaction. Scaling was evaluated 24 hours (day 3) after the last application of samples (day 2) according to the criteria described in Materials and Methods.

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