Histamine H_1 and H_2 Receptor Antagonists Accelerate Skin Barrier Repair and Prevent Epidermal Hyperplasia Induced by Barrier Disruption in a Dry Environment

Yutaka Ashida, Mitsuhiro Denda, and Tetsuji Hirao
Skin Biology Research Laboratories, Life Science Research Center, Shiseido Research Center, Yokohama, Japan

Keratinocytes have histamine H_1 and H_2 receptors, but their functions are poorly understood. To clarify the role of histamine receptors in the epidermis, we examined the effects of histamine receptor antagonists and agonists applied epicutaneously on the recovery of skin barrier function disrupted by tape stripping in hairless mice. Histamine H_2 receptor antagonists famotidine and cimetidine accelerated the recovery of skin barrier function, but histamine and histamine H_2 receptor agonist dimaprit delayed the barrier repair. Application of compound 48/80, a histamine releaser, also delayed the recovery. Imidazole, an analog of histamine, had no effect. The histamine H_1 receptor antagonists diphenhydramine and tripelennamine accelerated the recovery. Histamine H_3 receptor agonist N^{α}-methylhistamine and antagonist thioperamide had no effect. In addition, topical application of famotidine or diphenhydramine prevented epidermal hyperplasia in mice with skin barrier disrupted by acetone treatment in a dry environment (humidity < 10%) for 4 d. In conclusion, both the histamine H_1 and H_2 receptors in the epidermis are involved in skin barrier function and the cutaneous condition of epidermal hyperplasia. ***Key words: diphenhydramine/famotidine/itch/low humidity. J Invest Dermatol 116:261–265, 2001***

Histamine is well known as a chemical mediator that plays important roles in allergic inflammatory and immune reactions (Falus and Meretey, 1992). In skin, it is synthesized and stored in mast cells in the dermis but is also generated in keratinocytes (Malaviya *et al*, 1996). Histamine in the epidermis is derived from the keratinocyte itself and from mast cells in the dermis, but the role of histamine in the epidermis is still largely unknown. Histamine has three types of receptors. In skin, both the histamine H_1 receptor and histamine H_2 receptor exist (Greaves and Davies, 1982). The histamine H_1 receptor is considered to contribute to itch, and histamine H_1 receptor antagonists are clinically used for pruritus in patients with atopic dermatitis (Zuberbier and Henz, 1999). Keratinocytes have histamine H_2 receptors, but their function is not clearly understood (Fitzsimons *et al*, 1998). The Ca^{2+} concentration affects the quantity of histamine H_2 receptors on keratinocytes as well as the differentiation of keratinocytes (Fitzsimons *et al*, 1999). The histamine H_2 receptor also accelerates cell proliferation (Wang *et al*, 1997) and affects the immune system (Nielsen and Hammer, 1992). Attempts to assess the clinical efficacy of histamine H_2 receptor antagonists on psoriasis have not been successful (Nielsen, 1996). The existence and the role of the histamine H_3 receptor in skin are still unclear in humans (Kavanagh *et al*, 1998). In rats, however, the histamine H_3 receptor is involved in the autoregulation of histamine release on mast cells (Ohkubo *et al*, 1994), and the regulation of substance P release is also mediated via prejunctional histamine H_3 receptors located on peripheral endings of sensory nerves (Ohkubo *et al*, 1995).

It is well known that seasonal changes affect the condition of normal skin and inflammatory dermatoses. The low humidity during winter makes the skin condition worse (Wilkinson and Rycroft, 1992; Sauer and Hall, 1996), and it sometimes causes itch. Low humidity also stimulates epidermal DNA synthesis (Sato *et al*, 1998), and amplifies the hyperproliferative response to disruption of skin barrier function (Denda *et al*, 1998). The skin barrier function is the epidermal permeability barrier mechanism at the level of the stratum corneum, which allows life in a terrestrial dry environment. Acute barrier disruption by tape stripping elicits a homeostatic repair response in the epidermis. Substances that accelerate the recovery of the disrupted skin barrier have been reported to be effective against epidermal hyperplasia (Denda *et al*, 1997).

In this study, we examined whether histamine H_1 and H_2 receptor antagonists accelerate the recovery of disrupted skin barrier function and are effective against epidermal hyperplasia.

MATERIALS AND METHODS

Animals Hairless mice, 7–10 wk old (HR-1, Hoshino, Japan) were used. Before the experiment, animals were caged separately for at least 4 d. These cages were maintained in a room kept at 22°C–26°C with a relative humidity of 40%-70%. All experiments were approved by the Animal Research Committee of the Shiseido Research Center in accordance with the National Research Council (NRC) Guide (National Research Council, 1996).

Compounds Famotidine, cimetidine, diphenhydramine hydrochloride, tripelennamine hydrochloride, histamine dihydrochloride, imidazole, compound 48/80, and polyethylene glycol (MW 300) were purchased from Sigma (St. Louis, MO). N^{α}-methylhistamine dihydrochloride, thioperamide maleate, and dimaprit dihydrochloride were purchased from RBI (Natick, MA). The test compound was dissolved or suspended

Manuscript received May 22, 2000; revised October 25, 2000; accepted for publication November 1, 2000.

Reprint requests to: Shiseido Research Center, 2-12-1 Fukuura, Kanazawa-ku, Yokohama 236–8643, Japan; Email: yutaka.ashida@to.shiseido.co.jp

Abbreviation: TEWL, transepidermal water loss.

in the control vehicle, which was a mixture of polyethylene glycol:ethanol:distilled water 1:3:1 in order to increase the solubility of the compounds, which have different polarities. These test samples were used at a concentration of 5%, which was determined in a preliminary study, except for histamine, which was used at 0.1%, its pharmacologic concentration for histamine-induced itch. The pH was measured with a pH test paper (Toyo Roshi, Tokyo). The pH of each test sample was adjusted below 6.0 with HCl, because recovery of skin barrier function is impeded at a neutral pH (Mauro *et al*, 1998a).

Recovery of barrier function Barrier disruption was achieved by repeated applications of cellophane tape (Scotch Crystal Clear Tape, 3M, St. Paul, MN) on mouse flank skin. The procedure was terminated when transepidermal water loss (TEWL) levels reached 8.5 ± 1.5 mg per cm^2 per h. Normal TEWL is less than 0.3 mg per cm^2 per h. TEWL was measured by using an electrolytic water analyzer (Meeco, Warrington, PA). We disrupted the skin on both flanks of mice. Immediately after barrier disruption 100 μl of test sample was applied on one side, and medium was applied on the other side as a control. TEWL was measured before barrier disruption, immediately after barrier disruption, and at 3 h, 6 h, and 9 h after barrier disruption. The time points of the measurement were determined in a preliminary examination to be appropriate for the detection of the effect of the test compound. The barrier recovery results are expressed as percentage recovery because of variations from day to day in the extent of barrier disruption. In each animal the percentage recovery was calculated using the following formula: [1 - (TEWL at indicated time – baseline TEWL)/(TEWL immediately after treatment – baseline TEWL)] × 100%. All data were compared with data from simultaneously studied controls. To avoid scratching during the observation, we fixed the hind legs of the animal with flexible tape.

Low-humidity condition Animals were kept separately in 7.2 l cages in which the relative humidity was maintained at less than 10% with dry air. The temperature was the same in all cages (22°C–26°C), and fresh air was circulated 100 times per hour. Animals were kept out of the direct stream of air. The animal's behavior was not restricted during the experiments. The weight gain and food intake of animals kept in a dry condition was not different from that of those kept in a normal condition during the course of the study. The level of NH_3 was always below 1 ppm.

Epidermal hyperplasia with barrier disruption and exposure to a dry atmosphere We applied 100 μl of test sample per 6 cm^2 of flank skin of mouse, and applied medium on the other side as a control. We kept the aminals in a dry condition for 48 h before barrier disruption. The test sample was applied from the onset of the experiment, because the dry condition itself without barrier disruption also induces epidermal proliferation and hyperplasia (Sato *et al*, 1998). Then, the area of the flank skin was treated with acetone-soaked cotton balls, as described previously (Denda *et al*, 1998). The procedure was terminated when TEWL reached 1.2–1.8 mg per cm^2 per h. Immediately after barrier disruption 100 μl of a 5% test sample was applied again to the treated area, and the animals were kept in a dry condition for 48 h. At the end of the experiment, the animals were killed and the skin from the treated *versus* control flanks was removed. After fixation with 4% paraformaldehyde, full-thickness skin samples were embedded in paraffin, sectioned (4 μm), and processed for hematoxylin and eosin staining. On each section, 50 areas were selected at random; the thickness of the epidermis was measured with an optical meter, and the mean value was calculated. Measurements were carried out in an observer-blinded fashion. The results are represented as a proliferative percentage to intact skin.

Statistics Data are presented as mean ± SD. Statistical differences were determined by ANOVA and Fisher's protected least significant difference as *post hoc* test.

RESULTS

We first evaluated the effects of the antagonists of the three types of histamine receptor on barrier recovery. As shown in **Fig 1**, the histamine H_1 receptor antagonist diphenhydramine significantly accelerated barrier recovery after tape stripping (**Fig 1*A*,** 41% and 21% faster at 3 h and 6 h, respectively), and the H_2 receptor antagonist famotidine also accelerated barrier repair significantly (**Fig 1*B*,** 78%, 26%, and 12% faster at 3 h, 6 h, and 9 h, respectively). On the other hand, the histamine H_3 receptor antagonist thioperamide did not affect the barrier repair process (**Fig 1*C***). Additionally, we confirmed that the other histamine H_1 and H_2 receptor antagonists had similar effects on the barrier recovery (**Table I**). The histamine H_1 receptor antagonist tripelennamine significantly accelerated barrier recovery after tape stripping (204% faster at 3 h), and the H_2 receptor antagonist cimetidine also accelerated barrier repair significantly (12-fold and 119% faster at 3 h and 6 h, respectively).

We next evaluated the effects of the histamine receptor agonists, histamine releaser, and histamine analog. As shown in **Fig 2**, histamine itself delayed the barrier repair process significantly (**Fig 2*A***, 28% slower at 9 h), and the histamine H_2 receptor agonist dimaprit also delayed barrier recovery significantly (**Fig 2*B*,** 20% slower at 6 h). Furthermore, the histamine releaser compound 48/80 delayed the barrier repair process significantly (**Fig 2*C*,** 12% slower at 6 h). On the other hand, the histamine H_3 receptor agonist N^{α}-methylhistamine and histamine analog imidazole did not affect the barrier repair process (**Table I**). Scratching behavior was not observed during the experiments.

Finally, we tested whether histamine H_1 and H_2 receptor antagonists also have an effect on skin disorders *in vivo*. To quantify the effect of histamine receptor antagonists, we measured the epidermal thickness after barrier disruption with acetone in animals kept in a dry condition. As shown in **Fig 3**, famotidine significantly inhibited epidermal hyperplasia compared with the control, dose-dependently. The inhibition of epidermal hyperplasia by 1% and 5% famotidine was 43% and 78%, respectively. Also, 5% diphenhydramine inhibited it significantly (83%).

DISCUSSION

The results of this study suggest that both the histamine H_1 and histamine H_2 receptors contribute to the maintenance of skin barrier function. We also found that both types of histamine receptor antagonist inhibited epidermal hyperplasia with barrier disruption induced by acetone treatment in mice kept in a dry condition. Therefore, the histamine H_1 and H_2 receptors may

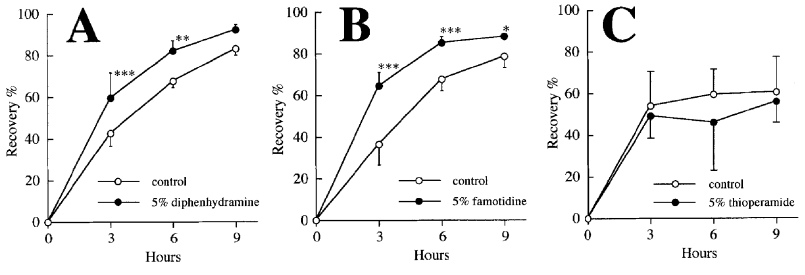

Figure 1. Histamine H_1 and H_2 receptor antagonists accelerate barrier recovery in mouse skin after tape stripping. Histamine H_3 receptor antagonist has no effect. The flank skin was treated until TEWL reached 8.5 ± 1.5 mg per cm^2 per h. Immediately after barrier disruption 100 μl of 5% diphenhydramine (*A*), 5% famotidine (*B*), 5% thioperamide (*C*), or control vehicle (polyethylene glycol:ethanol:distilled water 1:3:1) was applied to the treated area. TEWL was measured at the times indicated after barrier disruption. Data are presented as mean ± SD ($n = 4$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; p-values were calculated by ANOVA and Fisher's protected least significant difference as *post hoc* test.

contribute not only to skin barrier function but also to epidermal proliferation or inflammation. Moy *et al* (2000) reported that histamine altered vascular endothelial barrier function at cell-cell and cell-matrix sites, but the effects of histamine and histamine receptor antagonists on the epidermal barrier function were not reported. The mechanism of the efficacy of histamine H_1 and H_2 receptor antagonists on skin barrier function and skin condition also has not been elucidated.

Macroscopically, mast cell degranulation increases in a dry condition after acetone treatment (Denda *et al*, 1998). Histamine synthesis is also induced by ultraviolet (UV) B in keratinocytes (Malaviya *et al*, 1996). These findings imply that the histamine content in skin tissue increases during cutaneous inflammation. UV radiation enhances histamine sensitivity in keratinocytes, and prostaglandin synthesis in keratinocytes after UV radiation is mediated by histamine (Pentland *et al*, 1990). Histamine also enhances UVB-induced interleukin-6 (IL-6) production in keratinocytes (Shinoda *et al*, 1998). IL-6 is a proinflammatory cytokine, which may be responsible for mast cell differentiation and keratinocyte proliferation (Saito *et al*, 1996). Histamine accelerates cell proliferation (Wang *et al*, 1997) and IL-6 also accelerates it (Grossman *et al*, 1989). These reports suggest that histamine may regulate skin conditions. Although the results of many trials for oral application of histamine H_2 receptor antagonists to psoriasis with epidermal hyperplasia were not consistent, this study showed that epicutaneous application of histamine H_2 receptor antagonists may inhibit keratinocyte proliferation and accelerate barrier formation. Further study is needed to elucidate the function of histamine H_2 receptor in the epidermis.

We consider that itch may be one of the important factors that exacerbate the skin condition because scratching behavior results in disruption of skin barrier function. In our study, scratching was prevented during the barrier repair process. Thus, the effects of histamine H_1 and H_2 receptor antagonists were due to biochemical effects on the barrier homeostasis. Histamine H_1 receptor antagonists are used for the treatment of pruritus in patients with atopic dermatitis (Zuberbier and Henz, 1999). In addition, the histamine H_2 receptor antagonist inhibits the scratching behavior induced by histamine and compound 48/80 in mice (Inagaki *et al*, 1999). Therefore, the histamine H_2 receptor antagonist in combination with histamine H_1 receptor antagonist may not only accelerate barrier repair but also inhibit scratching behavior, which breaks the skin barrier. Schmelz *et al* (1997) reported that the microneurographic pattern of the response to histamine of histamine-sensitive c-fiber, which was mechanically insensitive, matched the time course of the itch sensation in the cutaneous branch of the peroneal nerve in humans. This type of c-fiber, which has very large innervation territories in skin, probably represents the afferent units long searched for mediating itch sensations (Schmelz *et al*, 1997). Further study is necessary to elucidate the various roles of histamine and the mechanism in skin including histamine H_3 receptors on mast cells and on peripheral endings of sensory nerves that may regulate substance P release (Ohkubo *et al*, 1995).

In this study we demonstrated that epicutaneous application of histamine H_1 and H_2 receptor antagonists accelerated the recovery of skin barrier function disrupted by tape stripping, and it also inhibited the epidermal hyperplasia with barrier dysfunction induced by acetone treatment in mice kept in a dry condition. Histamine and histamine receptor antagonists have effects on proliferation, differentiation, cytokine production and its release, and ion channels. The effects of histamine receptor antagonists via

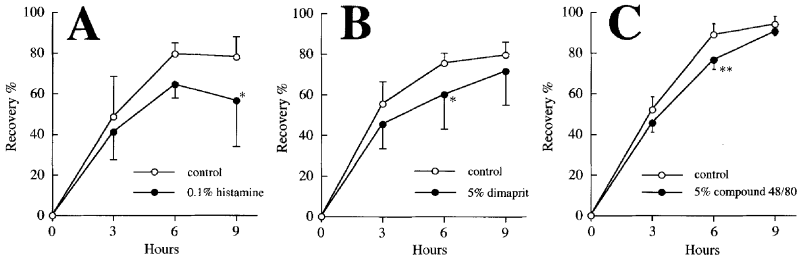

Figure 2. Histamine, histamine H_2 receptor agonist, and histamine releaser delay barrier recovery in mouse skin after tape stripping. The flank skin was treated until TEWL reached 8.5 ± 1.5 mg per cm^2 per h. Immediately after barrier disruption 100 µl of 0.1% histamine (*A*), 5% dimaprit (*B*), 5% compound 48/80 (*C*,) or control vehicle (polyethylene glycol:ethanol:distilled water 1:3:1) was applied to the treated area. TEWL was measured at the times indicated after barrier disruption. Data are presented as mean ± SD ($n = 4$). *$p < 0.05$,**$p < 0.01$; p-values were calculated by ANOVA and Fisher's protected least significant difference as *post hoc* test.

Table I. Effects of other histamine-related compounds on skin barrier recovery disrupted by tape stripping in mice[b]

		Recovery %[b]		
		3 h	6 h	9 h
histamine H_1 receptor antagonist				
tripelennamine	control	18.5 ± 20.3	46.5 ± 23.5	50.7 ± 28.7
	treatment	56.3 ± 12.4**	60.2 ± 14.3	66.0 ± 19.0
histamine H_2 receptor antagonist				
cimetidine	control	2.39 ± 10.8	23.4 ± 17.2	31.1 ± 12.9
	treatment	28.0 ± 17.2*	51.3 ± 26.5*	51.5 ± 12.3
histamine H_3 receptor agonist				
N^{α}-methylhistamine	control	48.1 ± 6.9	76.4 ± 5.7	88.4 ± 1.9
	treatment	43.5 ± 10.3	80.0 ± 1.7	87.5 ± 4.7
histamine analog				
imidazole	control	4.56 ± 15.1	39.7 ± 12.4	50.0 ± 14.4
	treatment	9.28 ± 18.0	28.7 ± 11.7	41.9 ± 14.5

[a]Recovery rate was measured as described in the *Materials and Methods*.

[b]Data are presented as mean ± SD (n = 4.8). *$p < 0.05$, **$p < 0.01$, p values were calculated by ANOVA and Fisher's protected least significant difference (Fisher's PLSD) as *post hoc* test.

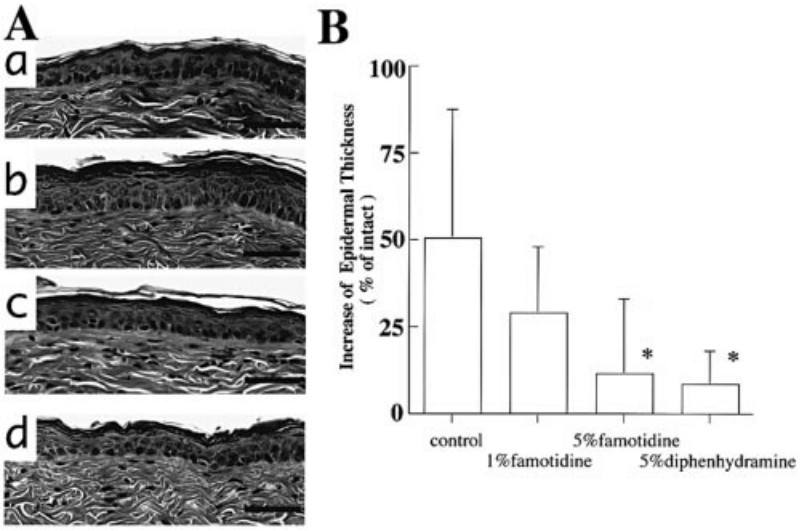

Figure 3. Both histamine H_1 receptor antagonist diphenhydramine and H_2 receptor antagonist famotidine prevent epidermal hyperplasia induced by acetone treatment of flank skin in mice kept in a dry condition. Hematoxylin and eosin staining (*A*), and increase of epidermal thickness (*B*). The barrier of the flank skin was disrupted by topical treatment with acetone until TEWL = 1.2–1.8 mg per cm^2 per h. Animals were maintained in a dry environment for 48 h before and 48 h after barrier disruption. A 100 μl volume of test sample or control vehicle (polyethylene glycol:ethanol:distilled water 1:3:1) was applied to the treated area at the beginning of the experiment and immediately after barrier disruption. (*A*) Intact (a), control (b), 5% diphenhydramine (c), 5% famotidine (d). *Scale bar*: 15 μm. (*B*) Data are presented as mean ± SD ($n = 5$). *$p < 0.05$; p-values were calculated by ANOVA and Fisher's protected least significant difference as *post hoc* test.

histamine H_1 or H_2 receptor on them have been reported for various tissues. Histamine-induced DNA synthesis is inhibited by H_1 receptor antagonists in carcinoma and melanoma cells that express histamine H_1 receptor (Tilly *et al*, 1990). Pyrilamine, a histamine H_1 receptor antagonist, blocks histamine-mediated UVB-induced IL-6 production in human keratinocytes (Shinoda *et al*, 1998). Histamine H_1 receptor antagonists block cardiac Na^+, Ca^{2+}, and K^+ channels (Delpon *et al*, 1999). On the other hand, cimetidine, a histamine H_2 receptor antagonist, reverses histamine-mediated increase in IL-1α-induced IL-1β synthesis in peripheral blood mononuclear cells (Vannier and Dinarello, 1993). Histamine suppresses IL-12 and stimulates IL-10 production in peripheral monocytes, and cimetidine antagonizes these effects (Elenkov *et al*, 1998). H_2 receptor antagonists reverse histamine-induced increase of IL-4, IL-5, and interferon-γ production in T cells (Krouwels *et al*, 1998). Cimetidine inhibits cell proliferation and *c-fos* gene transcription induced by histamine H_2 receptor activation in human embryonic kidney cells stably transfected with human H_2 receptor (Wang *et al*, 1997). Histamine and the selective histamine H_2 receptor agonist dimaprit reduced a specific K^+ current in myenteric neurons from guinea pig small intestine, and cimetidine suppressed it (Starodub *et al*, 2000). But, the roles of each type of histamine receptor in the epidermis are unknown, and the mechanism of barrier repair acceleration of histamine H_1 and H_2 receptor antagonists is also still unknown. The production of various kinds of cytokines like IL-1α and tumor necrosis factor α in keratinocytes increases after skin barrier disruption (Wood *et al*, 1992; Nickoloff and Naidu, 1994) and not only the production of epidermal IL-1α but also its release increases after skin barrier disruption (Wood *et al*, 1996). Therefore, the histamine H_1 and H_2 receptors may regulate skin conditions via these cytokines. Also the quantity of histamine receptor on keratinocytes may change with the skin condition. In this study the effects of histamine H_1 and H_2 receptor antagonists appear so early that they may be involved in the secretion of lamellar bodies, which are related to the epidermal calcium and potassium gradient (Lee *et al*, 1992; Menon *et al*, 1994). Mauro *et al* (1998b) showed an alteration of calcium and potassium localization immediately after barrier disruption. Topical application of calcium or potassium delayed the barrier recovery (Lee *et al*, 1992). Keratinocyte K^+ channels mediate Ca^{2+}-induced differentiation (Mauro *et al*, 1997). These reports suggest that calcium and potassium concentration in the epidermis strongly relates to epidermal barrier homeostasis. On the other hand, Koizumi and Ohkawara (1999) demonstrated that histamine H_2 receptor antagonist cimetidine specifically inhibited histamine-mediated increase in intracellular Ca^{2+} of cultured human keratinocytes significantly, although histamine H_1 receptor antagonist diphenhydramine did not inhibit it significantly. Moreover, some potassium currents are regulated by histamine H_2 receptor (Yazawa and Abiko, 1993; Adeagbo and Oriowo, 1998; Starodub *et al*, 2000). Fitzsimons *et al* (1999) reported that the quantity of histamine H_2 receptors changes with Ca^{2+} concentration in relation to differentiation in epidermal tumor cell lines. These reports also suggest that the differences in the function of histamine H_1 and H_2 receptors in the epidermis may depend on the regulation of calcium and potassium concentration in the epidermis. The roles of each histamine receptor in calcium and potassium concentration and ion transport including ion channels in the epidermis remain to be investigated. Furthermore, Lichey *et al* (1994) reported that histamine release is modulated by glycosphingolipids in basophils. But, the relationship between histamine receptors and lipid synthesis has not been clarified yet. A mechanistic study of the relationship between histamine receptors and the homeostatis of intercellular lipids in the stratum corneum should be carried out.

In conclusion, both the histamine H_1 and histamine H_2 receptors in the epidermis are involved in skin barrier function and the skin condition of epidermal hyperplasia.

REFERENCES

Adeagbo ASO, Oriowo MA: Histamine receptor subtypes mediating hyperpolarization in the isolated, perfused rat mesenteric pre-arteriolar bed. *Eur J Pharmacol* 347:237–244, 1998

Delpon E, Valenzuela C, Tamargo J: Blockade of cardiac potassium and other channels by antihistamines. *Drug Safety* 21 (Suppl. 1):11–18, 1999

Denda M, Kitamura K, Elias PM, Feingold KR: *trans*-4-(Aminomethyl) cyclohexane carboxylic acid (t-AMCHA), an anti-fibrinolytic agent, accelerates barrier recovery and prevents the epidermal hyperplasia induced by epidermal injury in hairless mice and humans. *J Invest Dermatol* 109:84–90, 1997

Denda M, Sato J, Tsuchiya T, Elias PM, Feingold KR: Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: Implication for seasonal exacerbations of inflammatory dermatoses. *J Invest Dermatol* 111:873–878, 1998

Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP, Wilder RL: Histamine potently suppresses human IL-12 and stimulates IL-10 production via H_2 receptors. *J Immunol* 161:2586–2593, 1998

Falus A, Meretey K: Histamine: an early messenger in inflammatory and immune reactions. *Immunol Today* 13:154–156, 1992

Fitzsimons C, Duran H, Labombarda F, Molinari B, Rivera E: Histamine receptor signalling in epidermal tumor cell lines with H-*ras* gene alterations. *Inflamm Res* 47 (Suppl. I):S50–S51, 1998

Fitzsimons C, Duran H, Engel N, Molinari B, Rivera E: Changes in H_2 receptor expression and coupling during Ca^{2+}-induced differentiation in mouse epidermal keratinocytes. *Inflamm Res* 48 (Suppl. I):S73–S74, 1999

Greaves MW, Davies MG: Histamine receptors in human skin: indirect evidence. *Br J Dermatol* 107 (Suppl. 23):101–105, 1982

Grossman RM, Krueger J, Yourish D, *et al*: Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. *Proc Natl Acad Sci* 86:6367–6371, 1989

Inagaki N, Nakamura N, Nagao M, Musoh K, Kawasaki H, Nagai H: Participation

of H_1 and H_2 receptors in passive cutaneous anaphylaxis-induced scratching behavior in ICR mice. *Eur J Pharmacol* 367:361–371, 1999

Kavanagh GM, Sabroe RA, Greaves MW, Archer CB: The intradermal effects of the H_3 receptor agonist Rα methylhistamine in human skin. *Br J Dermatol* 138:622–626, 1998

Koizumi H, Ohkawara A: H2 histamine receptor-mediated increase in intracellular Ca^{2+} in cultured human keratinocytes. *J Dermatol Sci* 21:127–132, 1999

Krouwels FH, Hol BEA, Lutter R, Bruinier B, Bast A, Jansen HM, Out TA: Histamine affects interleukin-4, interleukin-5, and interferon-γ production by human T cell clones from the airway and blood. *Am J Respir Cell Mol Biol* 18:721–730, 1998

Lee SH, Elias PM, Proksch E, Menon GK, Mao-Quiang M, Feingold KR: Calcium and potassium are important regulators of barrier homeostasis in murine epidermis. *J Clin Invest* 89:530–538, 1992

Lichey J, Zuberbier T, Luck W, Lau S, Wahn U: Influence of glycosphingolipids on the release of histamine and sulfidopepitide leukotrienes from human basophils. *Int Arch Allergy Immunol* 103:252–259, 1994

Malaviya R, Morrison AR, Pentland AP: Histamine in human epidermal cells is induced by ultraviolet light injury. *J Invest Dermatol* 106:785–789, 1996

Mauro T, Dixon DB, Komuves L, Hanley K, Pappone PA: Keratinocyte K^+ channels mediate Ca^{2+}-induced differentiation. *J Invest Dermatol* 108:864–870, 1997

Mauro T, Grayson S, Gao WN, *et al*: Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. *Arch Drmatol Res* 290:215–222, 1998a

Mauro T, Bench G, Sidderas-Haddad E, Feingold K, Elias P, Cullander C: Acute barrier perturbation abolishes the Ca^{2+} and K^+ gradients in murine epidermis: quantitative measurement using PIXE. *J Invest Dermatol* 111:1198–1201, 1998b

Menon GK, Price LF, Bommannan B, Elias PM, Feingold KR: Selective obliteration of the epidermal calcium gradient leads to enhanced lamellar body secretion. *J Invest Dermatol* 102:789–795, 1994

Moy AB, Winter M, Kamath A, *et al*: Histamine alters endothelial barrier function at cell-cell and cell-matrix sites. *Am J Physiol Lung Cell Mol Physiol* 278:L888–L898, 2000

National Research Council: *Guide for the Care and Use of Laboratory Animals*. 7th edn. Washington, DC: National Academic Press, 1996

Nickoloff BJ, Naidu Y: Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol* 30:535–546, 1994

Nielsen HJ: Histamine-2 receptor antagonists as immunomodulators: new therapeutic views? *Ann Med* 28:107–113, 1996

Nielsen HJ, Hammer JH: Possible role of histamine in pathogenesis of autoimmune diseases: implications for immunotherapy with histamine-2 receptor antagonists. *Med Hypotheses* 39:349–355, 1992

Ohkubo T, Shibata M, Inoue M, Kaya H, Takahashi H: Autoregulation of histamine release via the histamine H_3 receptor on mast cells in the rat skin. *Arch Int Pharmacodyn Ther* 328:307–314, 1994

Ohkubo T, Shibata M, Inoue M, Kaya H, Takahashi H: Regulation of substance P release mediated via prejunctional histamine H_3 receptors. *Eur J Pharmacol* 273:83–88, 1995

Pentland AP, Mahoney M, Jacobs SC, Holtzman J: Enhanced prostaglandin synthesis after ultraviolet injury is mediated by endogenous histamine stimulation. *J Clin Invest* 86:566–574, 1990

Saito H, Ebisawa M, Tachimoto H, *et al*: Selective growth of human mast cells induced by *steel* factor, IL-6, and prostaglandin E_2 from cord blood mononuclear cells. *J Immunol* 157:343–350, 1996

Sato J, Denda M, Ashida Y, Koyama J: Loss of water from the stratum corneum induces epidermal DNA synthesis in hairless mice. *Arch Dermatol Res* 290:634–637, 1998

Sauer GC, Hall JC. Seasonal skin diseases. In: Sauer GC, Hall JC: eds. *Manual of Skin Diseases*. Philadelphia: Lippincott-Raven, 1996:pp 23–28

Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjork HE: Specific C-receptors for itch in human skin. *J Neurosci* 17:8003–8008, 1997

Shinoda S, Kameyoshi Y, Hide M, Moriya E, Yamamoto S: Histamine enhances UVB-induced IL-6 production by human keratinocytes. *Arch Dermatol Res* 290:429–434, 1998

Starodub AM, Wood JD: Histamine suppresses A-type potassium current in myenteric neurons from guinea pig small intestine. *J Pharmacol Exp Ther* 294:555–561, 2000

Tilly BC, Tertoolen LG, Remorie R, Ladoux A, de Verlaan I, Laat SW, Moolenaar WH: Histamine as a growth factor and chemoattractant for human carcinoma and melanoma cells: action through Ca^{++}-mobilizing H_1 receptors. *J Cell Biol* 110:1211–1215, 1990

Vannier E, Dinarello CA: Histamine enhances interleukin (IL)-1-induced IL-1 gene expression and protein synthesis via H2 receptors in peripheral blood mononuclear cells. Comparison with IL-1 receptor antagonist. *J Clin Invest* 92:281–287, 1993

Wang L-D, Hoeltzel M, Butler K, Hare B, Todisco A, Wang M, Del Valle J: Activation of the human histamine H_2 receptor is linked to cell proliferation and *c-fos* gene transcription. *Am J Physiol* 273:C2037–C2045, 1997

Wilkinson JD, Rycroft RJ. Contact dermatitis. In: Burton JL, Ebling FJG: eds. *Champion Relative Humidity, Textbook of Dermatology*. 5th edn. Oxford: Blackwell Scientific Publications, 1992:pp 614–615

Wood LC, Jackson SM, Elias PM, Grunfeld C, Feingold KR: Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice. *J Clin Invest* 90:482–487, 1992

Wood LC, Elias PM, Calhoun C, Tsai JC, Grunfeld C, Feingold KR: Barrier disruption stimulates interleukin-1α expression and release from a pre-formed pool in murine epidermis. *J Invest Dermatol* 106:397–403, 1996

Yazawa K, Abiko Y: Modulation by histamine of the delayed outward potassium current in guinea-pig ventricular myocytes. *Br J Pharmacol* 109:142–147, 1993

Zuberbier T, Henz BM: Use of cetirizine in dermatologic disorders. *Ann Allergy Asthma Immunol* 83:476–480, 1999