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Physical and Chemical Factors that Improve Epidermal Permeability Barrier Homeostasis

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1. Introduction

For terrestrial creatures, the water-impermeable barrier function of the skin is essential to maintain life in the face of environmental dryness. Stratum corneum, which plays a crucial role in the barrier function, is composed of two components, i.e., protein-rich nonviable cells and intercellular lipid domains. When the barrier function is damaged by a surfactant, organic solvent or tape stripping, a series of homeostatic systems operates to restore the barrier function to its original level. At the first stage of the barrier repair process, exocytosis of lipid-containing granules, lamellar bodies, is accelerated and the internal lipid is secreted into the intercellular domain between the stratum granulosum and stratum corneum, forming a water-impermeable membrane.

The barrier function is strongly associated with skin pathology. Abnormality of the barrier function is observed in a variety of skin diseases, such as atopic dermatitis. Although the barrier function of healthy skin can recover automatically after damage, the recovery is delayed by emotional stress or by aging. Moreover, under low environmental humidity, barrier damage induces epidermal hyperplasia and inflammation.

On the other hand, acceleration of the barrier recovery prevents epidermal hyperplasia induced by barrier disruption in a dry environment. Thus, methods to improve the barrier function are very important for clinical dermatology. In the last two decades, various chemical and physical factors that accelerate the barrier recovery process have been reported. In this chapter, I will describe those findings and discuss some new biological aspects of epidermal barrier function.

2. Physical factors that influence barrier function

2.1 Temperature

2.1.1 Exposure to high temperature for one hour

Since the end of the last century, a series of thermo-activated receptors, called the transient receptor potential protein (TRP) superfamily, has been found in the peripheral nervous system and cloned. Julius and his co-workers found TRPV1 (VR1) as a polymodal detector of pain-producing heat (>43^{o}C) or chemicals, such as capsaicin and protons, in primary afferent neurons (Caterina et al. 1997). We showed that TRPV1 is also expressed in human epidermal keratinocytes (Denda et al. 2001), and demonstrated its functional activity in human cultured keratinocytes (Inoue et al. 2002). Subsequently, TRPV3 (Peier 2002a) and

TRPV4 (Chung et al. 2003), both of which are activated by high temperature (around 30°C), were also found to be expressed in keratinocytes.

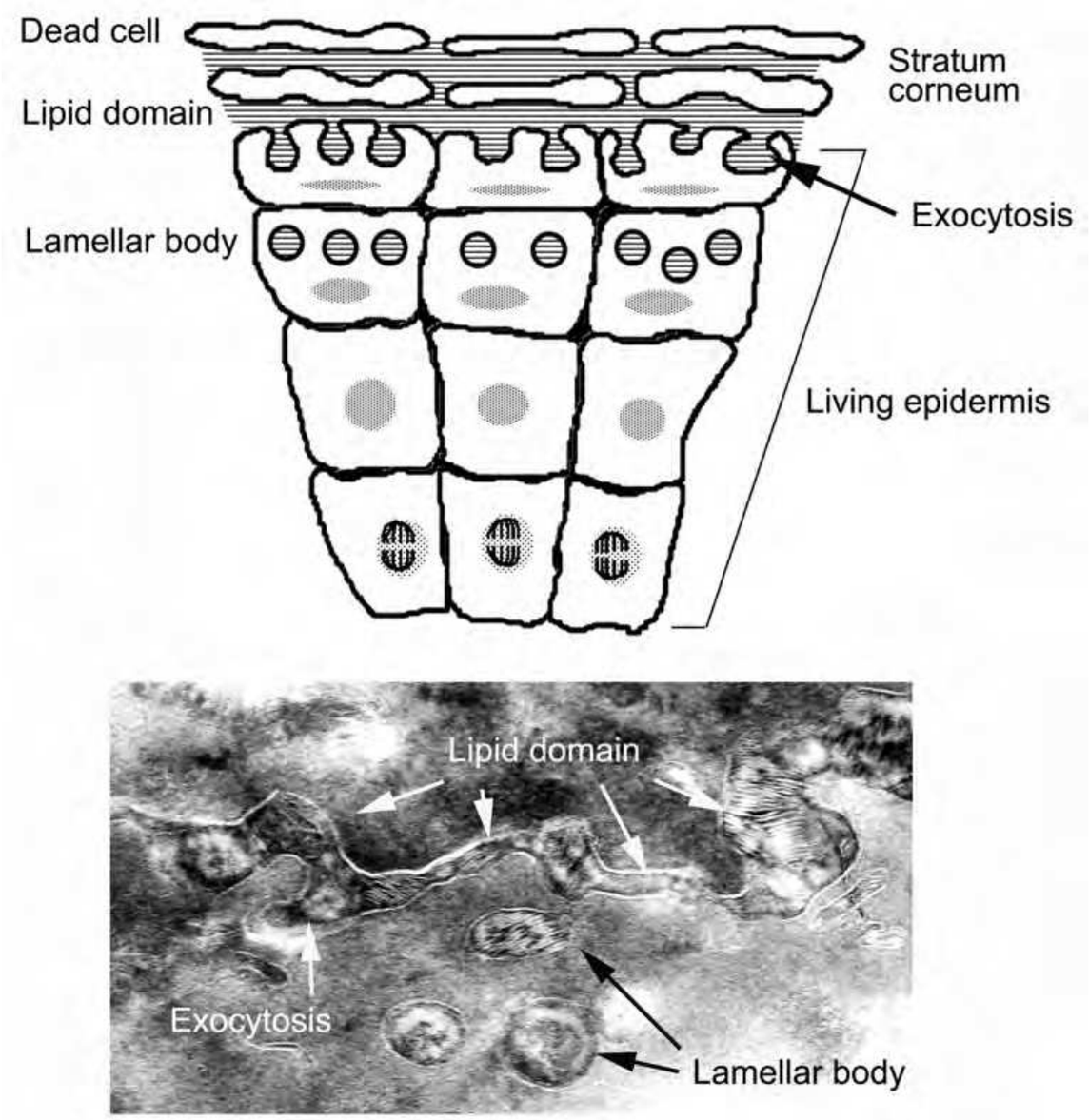

Fig. 1. Schematic diagram of skin (top) and photomicrograph illustrating the skin structures (bottom).

We have shown that changes of calcium dynamics are associated with epidermal permeability barrier homeostasis [Denda 2003a]. TRPs are cation-permeable channels. Thus, we hypothesized that activation of TRPs might influence barrier homeostasis. To evaluate the influence of these receptors on barrier homeostasis, we incubated hairless mouse skin and human skin at various temperatures immediately after tape stripping

(Denda 2007). At temperatures from 36°C to 40°C, barrier recovery was accelerated in both species compared with the area kept at 34°C. At 34°C or 42°C, barrier recovery at occluded sites was delayed compared with un-occluded sites. Topical application of 4α-phorbol 12,13-didecanone, an activator of TRPV4, accelerated barrier recovery, while ruthenium red, a blocker of TRPV4, delayed it. Capsaicin, an activator of TRPV1, delayed barrier recovery, while capsazepin, an antagonist of TRPV1, blocked this delay. 2-Aminoethoxydiphenyl borate and camphor, TRPV3 activators, did not affect the barrier recovery rate. Since TRPV4 is activated at about 35°C and above, while TRPV1 is activated at about 42°C and above, these results suggest that TRPV1 and TRPV4 both influence skin permeability barrier homeostasis.

2.1.2 Exposure to low temperature for one minute

Previous studies have identified cold-sensitive proteins, TRPA1 and TRPM8, that are activated by low temperature (<22°C) in peripheral nerve cells [Story 2003][Peier 2002b]. Recently, TRPA1 was also found in epidermal cells, in which it is activated by lower temperature (<17°C) [Atoyan 2009]. We demonstrated that exposure of cultured human keratinocytes to low temperature induced elevation of intracellular calcium [Tsutsumi 2010]. When the temperature of the medium was reduced to 17~22°C, elevation of intracellular calcium was observed. The extent of elevation was greater in non-differentiated cells than in differentiated cells. Application of Ruthenium Red (a non-selective TRP blocker) and HC030031 (a specific antagonist of TRPA1) reduced the elevation. These results suggest that functional cold-sensitive calcium channels, TRPA1and/or TRPM8, are present in human epidermal keratinocytes. Thus, we hypothesized that modulation of TRPA1 and/or TRPM8 might influence epidermal permeability barrier homeostasis.

To test this idea, we first examined the effects of topical application of agonists of TRPA1 and brief cold exposure on the barrier recovery rate after barrier disruption [Denda 2010a]. Topical application of a TRPA1 agonist, allyl isothiocyanate or cinnamaldehyde, accelerated the barrier recovery after tape stripping. The effect of both agonists was blocked by HC030031, an antagonist of TRPA1. Brief exposure (1 minute) to cold (10-15°C) also accelerated barrier recovery and this acceleration was also blocked by HC030031. Electron-microscopic studies indicated that brief cold exposure accelerated lamellar body secretion between stratum corneum and stratum granulosum, while pre-treatment with HC030031 inhibited the secretion. These results support the hypothesis that TRPA1 is associated with epidermal permeability barrier homeostasis.

We next examined the effect of topical application of TRPM8 modulators on epidermal permeability barrier homeostasis [Denda 2010b]. Immunohistochemical study and RT-PCR confirmed the expression of TRPM8 or TRPM8-like protein in epidermal keratinocytes. Topical application of TRPM8 agonists, menthol and WS 12, accelerated barrier recovery after tape stripping. The effect of WS12 was blocked by a non-selective TRP antagonist, Ruthenium Red, and a TRPM8-specific antagonist, BTCT. Topical application of WS12 also reduced epidermal proliferation associated with barrier disruption under low humidity, and this effect was blocked by BTCT. Our results indicate that TRPM8 or a closely related protein in epidermal keratinocytes plays a role in epidermal permeability barrier homeostasis and epidermal proliferation after barrier insult.

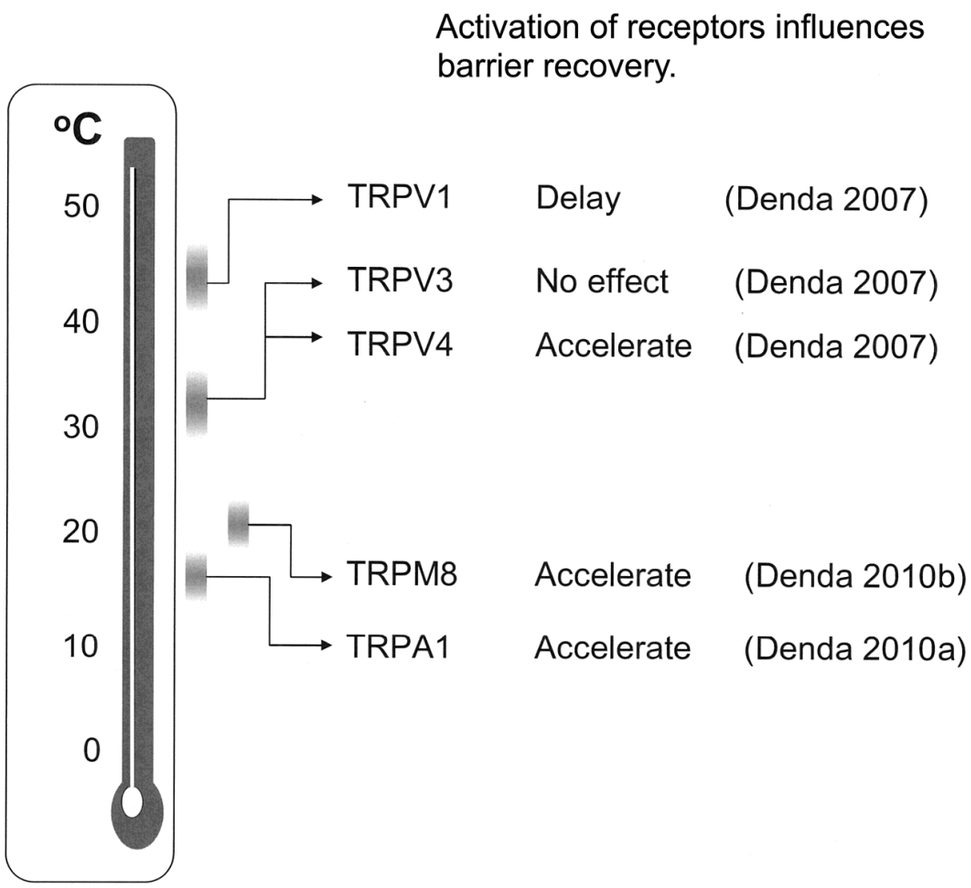

Fig. 2. Temperature ranges within which various TRP receptors are activated, and effect of their activation on epidermal permeability barrier homeostasis.

2.2 Visible light

The effects of ultraviolet or infrared radiation on skin are well known, but only a few reports describe the effect of visible radiation. We have shown that visible radiation influences the epidermal barrier recovery rate after barrier disruption (Denda & Fuziwara 2008). The effects of visible radiation on epidermal permeability barrier recovery were evaluated by using light-emitting diodes as light sources. The flank skin of hairless mice was tape-stripped, and immediately exposed to blue (430-510 nm), green (490-560 nm), red (550-670 nm) or white (400-670 nm) light (20 W each) for 1 hour, followed by measurement of transepidermal water loss. Control mice were kept in a dark box during the experiments. During the irradiation, the skin surface temperature was kept constant at 37°C in all mice. Irradiation with red light significantly accelerated barrier recovery, while irradiation with blue light delayed it, compared with the control. White or green light did not affect the barrier recovery rate. We next carried out a study using hairless mouse skin organ culture. The permeability barrier was disrupted by means of acetone treatment, then each section was incubated afloat on the medium (37°C) and irradiated with blue, red or white light (20 w) for one hour. Immediately after the end of irradiation, we evaluated the barrier

function. Again, red light accelerated barrier recovery, while blue light delayed it. An electron-microscopic study suggested that red light accelerated lamellar body secretion, while blue light blocked it. These results indicate that visible radiation affects skin barrier homeostasis. That is, epidermal keratinocytes might have a sensory system for visible radiation.

Rhodopsin is a well-known photosensitive protein found in rod cells of the retina and detects light/dark contrast. Cone opsins are also photosensitive receptors in the cone cells of the retina and detect color. We have reported immunochemical studies using anti-rhodopsin and anti-opsin antibodies on human skin (Tsutsumi 2009). Both mouse retina and human epidermis showed clear immunoreactivity with each antibody. Interestingly, immunoreactivity against longer-wavelength opsin antibody was observed in the basal layer of the epidermis, while immunoreactivity against rhodopsin and shorter-wavelength opsin was observed in the upper layer. PCR analysis confirmed the expression of rhodopsin-like and opsin-like genes in human retina and skin. These results suggest that a series of proteins, which play a crucial role in visual perception, are also expressed in human epidermis.

In retina, transducin and phosphodiesterase 6 play key roles in signal transmission. Thus, we hypothesized that these proteins might exist in epidermal keratinocytes and be associated with barrier homeostasis (Goto 2011). Immunohistochemical study and reverse transcription-PCR assays confirmed the expression of both transducin and phosphodiesterase 6 in epidermal keratinocytes. Topical application of 3-isobutyl-1-methylxanthine, a non-specific phosphodiesterase inhibitor, blocked the acceleration of barrier recovery by red light. Topical application of zaprinast, a specific inhibitor of phosphodiesterases 5 and 6, also blocked the acceleration, while T0156, a specific inhibitor of phosphodiesterase 5, had no effect. Red-light exposure reduced the epidermal hyperplasia induced by barrier disruption under low humidity, and the effect was blocked by pretreatment with zaprinast. Our results indicate phosphodiesterase 6 is involved in the recovery-accelerating effect of red light on the disrupted epidermal permeability barrier. Also, epidermal keratinocytes have a similar energy conversion system to that of the retina.

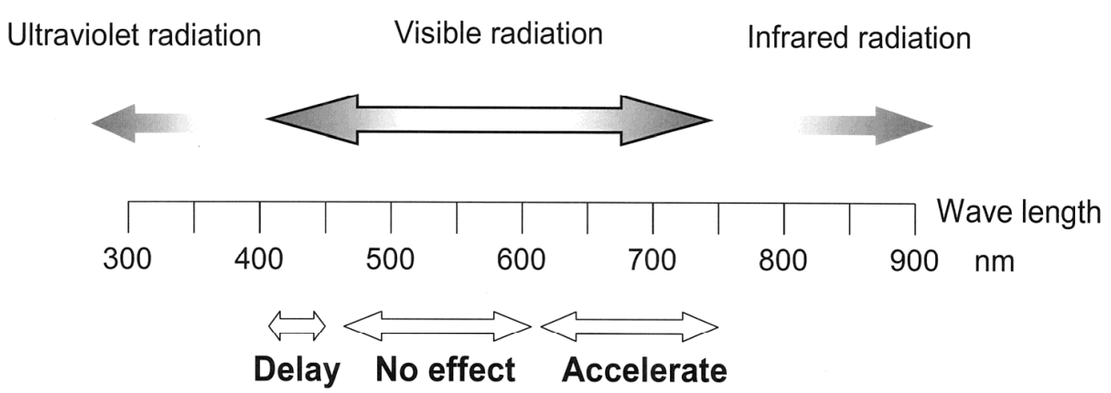

Fig. 3. Effects of visible radiation on epidermal permeability barrier homeostasis.

2.3 Sound

The frequency range of audible acoustic sound for adult humans is approximately 20-16000 Hz (Heffner 2004). However, Oohashi and his coworkers demonstrated that ultrasound at a frequency above 20000 Hz (20 kHz) influences human brain electrical activity and systemic hormonal levels (Oohashi 2000)(Oohashi 2006)(Kawai 2001)(Yagi 2003). Interestingly, these effects did not involve the ear (Oohashi 2006). On the other hand, recent work has demonstrated that a slight, inaudible puff of air on the skin influences auditory perception (Gick & Derrick 2009). These results suggest that an unknown system that is responsive to ultrasound exists at the human body surface. Based on these findings, we considered that audible or inaudible sound frequencies might influence epidermal barrier homeostasis.

First, we evaluated the effects of 5, 10, 20 and 30 kHz sound on intact skin of hairless mice (Denda & Nakatani 2010). We disrupted the permeability barrier by tape stripping and immediately exposed the skin to sound for one hour. The speaker cone lightly touched one side of the flank, and we attached a silent speaker cone to the other flank as a control. Application of sound at a frequency of 10, 20 or 30 kHz accelerated barrier recovery, while 5 kHz sound had no effect. The effects on barrier recovery were observed 23 hours after cessation of the sound application.

To determine whether the effect was induced by sound or skin vibration, we next placed the speaker 1 or 3 cm away from the skin surface. In this case, too, significant acceleration of the barrier recovery by sound was observed. The sound pressure levels were 0 cm: 83 dB, 1 cm: 78 dB, 3 cm: 70 dB.

We also evaluated the effect of different sound pressures on the barrier recovery rate. The sound source was placed 1 cm away from the skin surface, and the frequency was 20 kHz. The barrier recovery rate increased with increasing sound pressure. An electron-microscopic study indicated that exposure to sound at a frequency of 20 kHz accelerated lamellar body secretion between stratum corneum (SC) and stratum granulosum (SG). These results indicate that epidermis might have an unknown system for sensing sound.

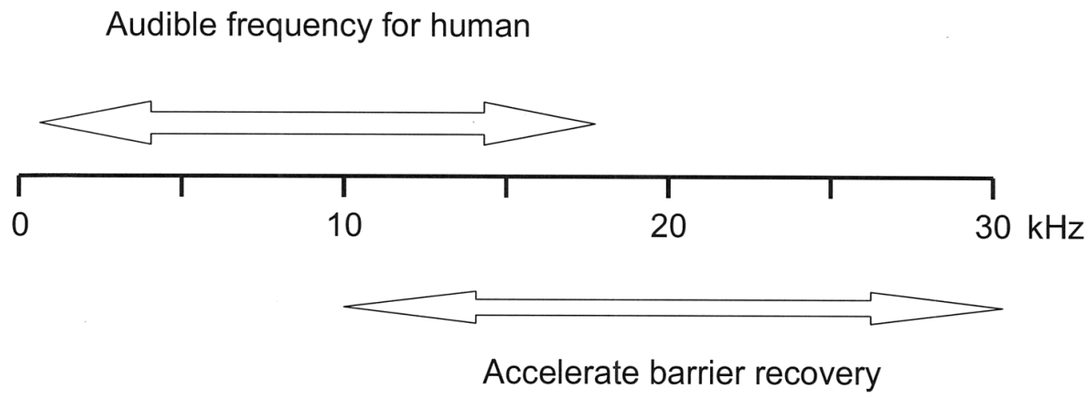

Fig. 4. Effects of sound on epidermal permeability barrier homeostasis

2.4 Electrical potential

It has been demonstrated that cultured human keratinocytes migrate to the negative pole in direct current electrical fields (Nishimura 1996). This result suggested that keratinocytes might have a sensory system for the external electrical field. Thus, we hypothesized that external electrical potential would influence epidermal barrier homeostasis. We applied negative and positive direct electric potential (0.5 V) to hairless mouse flank skin immediately after barrier disruption for one hour, and then we evaluated barrier recovery by the measurement of transepidermal water loss. At the area of applied negative potential, the barrier recovery rate was significantly accelerated, while the recovery was delayed at the area of positive applied potential (Denda & Kumazawa 2002).

We subsequently found that several interfacial electrical conditions also affect barrier homeostasis. For example, topical application of barium sulfate or aqueous solution of ionic polymers formed an electrical double layer on the skin surface and affected the barrier recovery rate (Fuziwara 2004)(Denda 2005). Moreover, just placing metals on the skin surface after barrier disruption accelerated the barrier recovery, presumably because free electrons were supplied from metal to the skin surface (Denda & Kumazawa 2010). When chemically different materials are in contact, electro-chemical phenomena, such as formation of an electrical double layer, are induced. We previously demonstrated that a voltage-gated calcium channel is expressed at the upper layer of the epidermis (Denda 2006). Thus, when the skin touches other materials, physiological phenomena might be induced.

3. Chemical factors that influence barrier function

3.1 Ions

Lipid metabolism is regulated by a series of enzymes in the epidermis (Feingold & Elias 2000) and each of them has optimal conditions of pH (Mauro 1998), concentrations of other ions (Denda 1999), etc. for activity. For example, the pH value of the healthy stratum corneum is kept acidic because the lipid-processing enzymes have an acidic optimal pH. Mauro et al. demonstrated that topical application of a basic buffer after barrier disruption delayed the repair process because the basic condition perturbed lipid processing (Mauro 1998).

It has also been shown that topical application of calcium or potassium reduced barrier repair [Lee 1992], while magnesium and a mixture of calcium and magnesium salts accelerated the repair process [Denda 1999]. Topical application of an aqueous solution containing 10 mM magnesium chloride, magnesium sulfate, and magnesium lactate accelerated barrier repair. Application of magnesium bis(dihydrogen phosphate) or magnesium chloride in PBS solution did not affect the barrier recovery rate. Application of 10 mM calcium chloride aqueous solution delayed barrier repair, but a mixture of calcium chloride and magnesium chloride accelerated it when the calcium-to-magnesium molar ratio was lower than 1. Application of the mixture also improved the condition of dry, scaly skin induced by SDS treatment. These results suggest that ions are important in barrier homeostasis.

3.2 Hexose

Hexose is known to influence the stability of phospholipid bilayers. Therefore, the effects of topical application of all 12 stereoisomers of dextro-hexose on the epidermal barrier recovery rate after barrier disruption were evaluated (Denda 2011). Immediately after tape stripping, a 0.1 M aqueous solution of each hexose was applied on hairless mouse skin. Among the 8 dextro-aldohexoses, topical application of altose, idose, mannose and talose

accelerated barrier recovery, while allose, galactose, glucose and gulose had no effect. Among the 4 dextro-ketohexoses, psicose, fructose, sorbose and tagatose all accelerated barrier recovery. Because the effects of hexoses on the barrier recovery rate appeared within one hour, the mechanism is unlikely to be genomic. Instead, these hexoses may influence phase transition of the lipid bilayers of lamellar bodies and cell membrane, a crucial step in epidermal permeability barrier homeostasis.

3.3 Physiological lipids

Lipids play a crucial role in the water-impermeable barrier function of the skin. Damaged barrier function can be restored by topical application of a water-impermeable substance such as petrolatum (Man 1995). In this case, the petrolatum stays in the stratum corneum and forms a water-impermeable membrane. However, Man et al. demonstrated that a topically applied mixture of stratum corneum lipids, i.e., ceramide, cholesterol and free fatty acids, was incorporated in the nucleated layer of epidermis and accelerated repair of the barrier function after damage (Man 1996). They were the first to report a method to accelerate the barrier recovery by regulating endogenous factors in the epidermis. Interestingly, when they applied ceramide, cholesterol, or free fatty acid alone, or a mixture of two of these, the barrier recovery was delayed. Only when they applied a mixture of all three lipids at a specific relative ratio was the barrier recovery accelerated (Man 1996). These results suggest that a balance of the three lipids is crucial for skin barrier homeostasis.

Physical factors	Accelerate barrier recovery	Delay barrier recovery
Temperature (Denda 2007)	36~40°C (1 hour)	>42°C
(Denda 2010a,b)	10~15°C (1 min)	
Visible light (Denda 2008)	Red (550~670 nm)	Blue (430~510 nm)
Electrical potential (Denda&Kumazawa 2002)	Negative	Positive
Sound (Denda&Nakatani 2010)	10~30 kHz	
Chemical factors		
Ionic polymers (Denda 2005)	sodium salt anionic	cationic
Barium sulphate (Fuziwara 2004)	ζ negative	ζ positive
Metal (Denda& Kumazawa 2010)	Pt, Au, Ag, In, Zr, Sm	
Ions (Lee 1991) (Denda 1999)	magnesium	calcium, potassium
Hexose (Denda 2011)	most hexoses	
Physiological lipids balanced mixture (Man 1996)	balanced mixture	unbalanced mixture

Table 1. Summary of the effects of physical, chemical and biological factors on skin permeability barrier recovery.

In the case of aging, different treatment might be necessary because of the different metabolism of aged skin. Ghadially et al. demonstrated that skin barrier function in elderly subjects was destroyed more easily than that in young individuals (Ghadially 1995). Moreover, the barrier recovery rate after barrier disruption was significantly slower for the elderly subjects than for younger ones. The same tendency was observed in both humans and hairless mice. They also suggested that synthesis of cholesterol is reduced more than that of other lipids, i.e., ceramide and fatty acids, in aged mice. The delay of barrier recovery

with aging was improved by topical application of cholesterol (Ghadially 1996) or mevalonic acid (Haratake 2000), presumably because the delay of the aged skin was caused by a decrease of cholesterol synthesis.

4. Biochemical factors that influence barrier function

4.1 Endocrine factors

Sex hormones are strongly associated with epidermal permeability barrier homeostasis (Hanley 1996). Moreover, when the balance of these hormones alters at menopause or during the menstrual cycle, skin sensitivity or barrier function is changed. These results suggest that the relative composition of hormones influences barrier function and skin sensitivity. We recently studied the effects of topical application of sex hormones on the permeability barrier recovery rate of hairless mice after tape stripping (Tsutusmi and Denda 2007). Application of androgens, testosterone and androsterone, delayed barrier recovery. The delay was blocked by application of beta-estradiol. Application of progesterone also delayed barrier recovery. However, the delay was enhanced by the application of beta-estradiol. These results suggest that the alteration of the sex hormone balance at menopause or during the estradiol cycle might be the cause of skin problems at the corresponding period of time.

4.2 Neurotransmitters

Epidermal keratinocytes express a series of receptors, which were originally found in the central nervous system as neurotransmitter receptors. These receptors can be categorized two groups: ionotropic receptors and G-protein-coupled receptors.

Among the former group, receptors that act as calcium ion or chloride ion permeable channels plays crucial roles in epidermal permeability barrier homeostasis. Topical application of calcium channel agonists delays barrier recovery, while antagonists accelerate barrier repair (Denda et al. 2002a) (Denda 2003) (Fuziwara 2003). Topical application of chloride ion channel agonists accelerates barrier recovery (Denda 2003) (Denda 2002b).

The G-protein coupled receptors influence intracellular cAMP level, which plays a crucial role in epidermal barrier homeostasis (Denda 2003b). Increase of intracellular cAMP in epidermal keratinocytes by topical application of forskolin delays barrier recovery, while cAMP antagonist treatment accelerates barrier recovery. Activation of dopamine 2-like receptors (Fuziwara 2005), melatonin receptors, and serotonin receptor (type 5-HT1) decreases intracellular cAMP and consequently accelerates barrier recovery, while activation of adrenergic β2 receptors increases the intracellular cAMP and delays barrier repair (Denda 2003b). Barrier disruption induces an increase of intracellular cAMP. Thus, topical application of agonists of receptors that reduce the intracellular cAMP level accelerates barrier repair. (Denda 2004, Denda 2005)

Histamine receptors are related to skin barrier function [Ashida and Denda 2001]. Three different types of histamine receptors, H1, H2, H3, and H4 have been reported. First, topical application of histamine H1 and H2 receptor antagonists accelerated barrier repair. Histamine itself, H2 receptor agonist, and histamine releaser delayed barrier repair. Histamine H3 receptor antagonist and agonist did not affect the barrier recovery rate. Topical application of H1 and H2 receptor antagonists prevented the epidermal hyperplasia induced by barrier disruption under low humidity. The mechanism of the

interactions between the histamine receptors and the barrier repair process have not been elucidated yet

Nitric oxide (NO) is also involved in barrier homeostasis. We first demonstrated that neuronal nitric oxide synthase knockout ($nNOS^{-/-}$) mice showed a faster barrier recovery rate than did wild-type mice. nNOS is expressed in epidermal keratinocytes [Ormerod 1998]. Thus, NO generated by keratinocytes might delay barrier repair. To examine this possibility, we next evaluated the effects of NO donor and NOS inhibitor on the barrier recovery rate. Topical application of a NO donor, S-nitroso-N-acetyl-D,L-penicillamine delayed barrier recovery. The application of a nNOS inhibitor accelerated barrier recovery, while the application of a inducible nitric oxide synthase (iNOS) inhibitor did not affect it. Moreover, topical application of a guanylyl cyclase inhibitor accelerated barrier recovery. We observed the release of NO from a skin organ culture after barrier disruption. Thus, regulation of nNOS in epidermal keratinocytes might be useful approach to improve barrier homeostasis (Ikeyama 2007).

Ionotropic receptors	Accelerate Barrier Recovery	Delay Barrier Recovery
P2X receptor (Denda 2002a)	Antagonist	Agonist
NMDA receptor (Fuziwara 2003)	Antagonist	Agonist
Cholinergic receptor (Denda 2003)	Antagonist	Agonist
GABA(A) receptor (Denda 2002b)	Agonist	-
Glycine receptor (Denda 2003)	Agonist	-
G-Protein coupled receptors		
Adrenergic β2 receptor (Denda 2003b)	Antagonist	Agonist
Dopamine 2-like receptor (Fuziwara 2005)	Agonist	Antagonist
Serotonin receptor (Denda 2005)	Agonist	-
Melatonin receptor (Denda 2005)	Agonist	-

No effect, or experiment has not been done.

Table 2. Effects of agonists and antagonists of neurotransmitter receptors on skin permeability barrier recovery.

Ryanodine receptors (RyR) play an important role as calcium channels in the regulation of intracellular calcium levels in the nervous system and muscles. We investigated the expression of RyR in human epidermis. (Denda 2011) Immunohistochemical studies and RT-PCR indicated the expression of RyR type 1, 2, and 3 proteins in epidermal keratinocytes. The expression level of each RyR subtype was higher in differentiating keratinocytes than in proliferative cells. We also demonstrated the functional expression of RyR by means of calcium imaging. In cultured human keratinocytes, application of the RyR agonist 4-chloro-*m*-cresol (CMC) induced elevation of the intracellular calcium concentration and co-application of the RyR antagonist 1,1′-diheptyl-4,4′-bipyridinium dibromide (DHBP) blocked the elevation. Application of CMC accelerated keratinocyte differentiation *in vitro*. On the other hand, topical application of CMC after tape-stripping of hairless mouse skin delayed barrier recovery, while application of an RyR antagonist,

dantrolene or DHBP, accelerated the barrier recovery. These results suggest that RyR expressed in epidermal keratinocytes is associated with both differentiation of keratinocytes and epidermal barrier homeostasis (Denda S 2011).

4.3 Protease inhibitors

Topical application of specific protease inhibitors accelerates barrier recovery after barrier disruption (Denda 1997). Topical application of 4-(aminomethyl)cyclohexane carboxylic acid (tranexamic acid), a well known anti-plasmin reagent, also accelerates barrier recovery. In contrast, inactive analogs of tranexamic acid do not influence barrier recovery. Application of several trypsin-like serine protease inhibitors, e.g., leupeptin, TLCK and PMSF, accelerates barrier recovery, while other protease inhibitors, e.g., EDTA, pepstatin, N-ethylmaleimide, chymostatin, and TPCK, have no effect on barrier recovery. Although the mechanism was not clarified, it was shown that protease activated receptor type 2 is associated with barrier homeostasis (Hachem 2006).

4.4 Nuclear hormone receptor activators

Feingold and his co-workers demonstrated an important influence of nuclear hormone receptors on epidermal differentiation and stratum corneum barrier formation. Activation of PPARα by farnesol stimulated the differentiation of epidermal keratinocytes (Feingold 1999)(Hanley 2000). Cornified envelope formation and involucrin and transglutaminase protein and mRNA levels were also increased by the activation of PPARα (Feingold 2000). Interestingly, the inflammatory response was also inhibited (Sheu 2002). Topical application of PPARα activators accelerated barrier recovery after tape stripping or acetone treatment and prevented the epidermal hyperplasia induced by repeated barrier disruption (Feingold 1999). Regulation of nuclear hormone receptors might therefore be a possible approach for improvement of the cutaneous barrier.

5. Psychological factors that influence barrier function

As described above, psychological stress impairs barrier homeostasis. To study the effects of stress on barrier homeostasis, we used three models of stress, i.e., immobilization, a crowded environment and a change of living place [Denda 1998][Denda 2000]. In each case, the barrier recovery rate was delayed after barrier disruption. The plasma corticosterone level was increased by each stress, and it was reduced by application of a sedative drug [Denda 2000]. The delay of barrier repair induced by psychological stress was also prevented by application of a sedative drug or glucocorticoid receptor antagonist [Denda 2000]. These results suggest that psychological stress stimulates increased production of glucocorticoids, which adversely affect skin barrier homeostasis. The effect of psychological stress on skin barrier homeostasis in humans has also been examined [Garg 2001]. Reduction of psychological stress might accelerate the skin barrier repair process. Several studies have demonstrated that certain odorants can reduce stress, acting like a sedative drug [Tsuchiya 1992]. These odorants prevented the delay in skin barrier recovery induced by psychological stress in both mice and humans [Denda 2000a][Denda 2000b]. These results suggest the feasibility of a new skin care strategy based on inhalation of specific odorants.

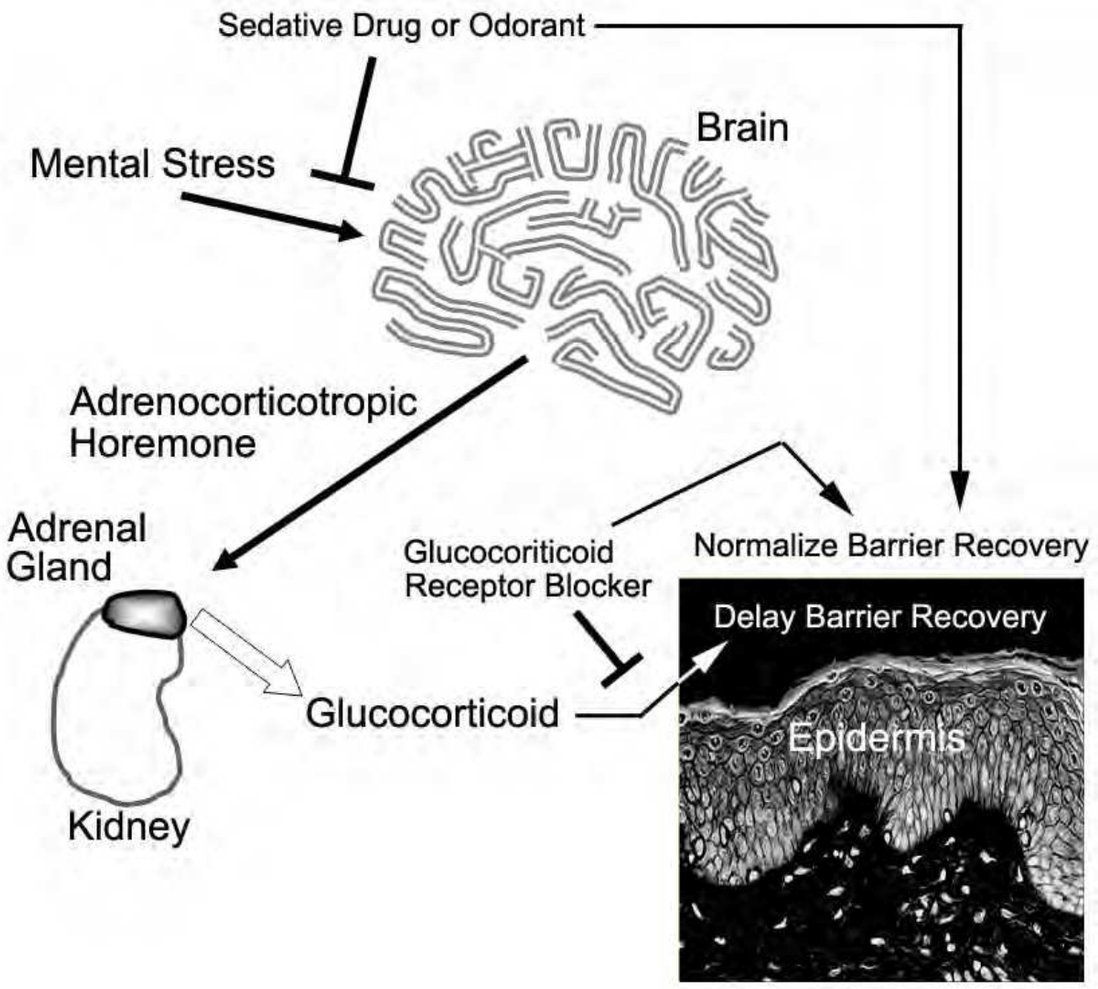

Fig. 5. Schematic illustration of the effect of mental stress on the endocrine system and on skin barrier function.

6. Conclusion

Epidermal barrier dysfunction is observed in a variety of skin diseases, such as atopic dermatitis, psoriasis, and contact dermatitis, and barrier disruption induces an inflammatory response that might aggravate dermatitis (Grice 1980). On the other hand, acceleration of barrier recovery was shown to improve epidermal hyperplasia (Denda 1997)(Fuziwara 2004). Since a wide range of physical or chemical factors, as described here, influence barrier homeostasis, control or modulation of these factors is expected to open up new possibilities for the treatment of human skin diseases involving barrier abnormality.

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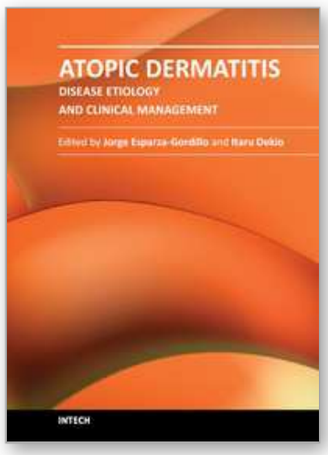

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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