INVESTIGATIVE REPORT

Surfactant-induced Chronic Pruritus: Role of L-Histidine Decarboxylase Expression and Histamine Production in Epidermis

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Shampoo and cleansers containing anionic surfactants including sodium dodecyl sulphate (SDS) often cause pruritus in humans. Daily application of 1–10% SDS for 4 days induced hind-paw scratching (an itch-related behaviour) in a concentration-dependent manner, and 10% SDS also caused dermatitis, skin dryness, barrier disruption, and an increase in skin surface pH in mice. SDS-induced scratching was inhibited by the opioid receptor antagonist naloxone and the H_1 histamine receptor antagonist terfenadine. Mast-cell deficiency did not inhibit SDS-induced scratching, although it almost completely depleted histamine in the dermis. Treatment with SDS increased the histamine content of the epidermis, but not that of the dermis. SDS treatment increased the gene expression and post-translation processing of L-histidine decarboxylase in the epidermis. The present results suggest that repeated application of SDS induces itch through increased production of epidermal histamine, which results from an increase in the gene expression and post-translation processing of L-histidine decarboxylase. ***Key words: sodium dodecyl sulphate; itch; mast cells; keratinocytes; L-histidine decarboxylase.***

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Many cleansers contain surfactants, and repeated exposure to surfactants can cause various adverse reactions in the skin, such as erythema, skin dryness and itching. In fact, the majority of adverse cutaneous reactions to personal care products are presumed to be caused by surfactants (1, 2). Surfactants irritate the skin through several mechanisms, including interaction with keratin (3) and alteration of lipid structure and barrier function (4, 5). Cutaneous irritation is dependent on the duration and frequency of surfactant exposure as well as the concentration and type of surfactant.

Surfactants are categorised into 4 primary groups according to the charge of their hydrophilic head: anionic, cationic, amphoteric, and non-ionic. Anionic surfactants, which chemically possess a negatively charged hydrophilic head, are commonly used in soaps and detergents because of their high detergency. Therefore, exposure to anionic surfactants occurs almost daily. The most frequently reported subjective symptom in surfactant users is itching (1). Itch-induced vigorous scratching damages the skin, causing irritation and dryness that worsen cutaneous lesions and increase itch. It is generally assumed that anionic substances, such as poly-L-lysine and morphine, degranulate mast cells to release histamine, an itch mediator (6). However, we have recently found that a single topical application of sodium laurate, an alkaline anionic surfactant, to murine skin increases scratching 2 h post-application and that the effect is not mediated by mast cell degranulation but rather by increased histamine production in epidermal keratinocytes (7). We have also shown that inhibition of histamine production by topical medical application can relieve acute scratching induced by topical application of sodium laurate (8). These findings suggest that histamine produced by keratinocytes plays an important role in pruritus arising after washing the skin with anionic surfactants.

Sodium dodecyl sulphate (SDS), a neutral anionic surfactant found in many shampoos and cleansers, causes irritant reactions in human and animal skin (9–11). Repeated topical application of 10% SDS induces various adverse skin reactions, such as dermatitis, skin dryness, and barrier disruption (11). In this study, we first examined whether the repeated topical application of 10% SDS would cause pruritus in mice, and next determined whether histamine released from mast cells and/or keratinocytes would be involved in the pruritogenic action of SDS.

MATERIALS AND METHODS

Animal

Male Slc:ICR mice were used at 7–8 weeks of age, and in a separate series of experiments, male mast-cell deficient mice (WBB6F1-*W/W^v*) and normal littermates (WBB6F1-+/+) were used at 7 weeks of age. For other details see Appendix S1[1].

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SDS treatment

The rostral part of the mouse back was shaved at least 3 days prior to the start of the experiment. SDS and *N*-lauroylsarcosine sodium salt (Nacalai Tesque, Inc., Kyoto, Japan) were dissolved in distilled water. SDS (10% w/v, pH 6.5) or *N*-lauroylsarcosine sodium salt solution (10% w/v, pH 7.7) was applied topically to the shaved skin in a volume of 50 µl; in one series of experiments 0.1%, 1%, and 10% SDS were applied. Topical application of these solutions was repeated at 24-h intervals for 4 days. The severity of dermatitis was scored as follows: 0 : no lesion; 1: subtle erythema; 2: mild erythema; 3: severe erythema and haemorrhage.

Assessment of skin dryness and cutaneous barrier disruption

Skin dryness was investigated by measuring stratum corneum (SC) hydration with a moisture checker (MY-808S; Scalar Corp., Tokyo, Japan); the level of hydration was expressed as relative capacitance. The cutaneous barrier was investigated by measuring transepidermal water loss (TEWL) with a vapor meter (VapoMeter®, model SWL4002; Keystone Scientific Co., Ltd. Tokyo, Japan). Each parameter was determined the day before the first application of surfactant solution and 22–24 h after each application.

Evaluation of scratching behaviour

Observation of scratching behaviour was performed as described previously (12, 13). A series of the following movements was counted as one bout of scratching: mice stretching the hind paw toward the treated site, leaning the head toward the hind paw, rapidly moving the hind paw several times, and then moving it to the floor (13). Hind-paw scratching behaviour directed towards the surfactant-treated site was observed for 1 h on the day before the first application of surfactant solution, 2 h after the first application, or 22–24 h after each application.

Administration of drugs

Terfenadine (Sigma, St. Louis, MO, USA) was dissolved in tap water containing 0.5% sodium carboxymethyl cellulose (Wako Pure Chemical Industries, Osaka, Japan) and administered orally at a dose of 30 mg/kg 30 min before the start of behavioural observation. Naloxone (Sigma) was dissolved in physiological saline (Ohtsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and administered subcutaneously at a dose of 1 mg/kg 15 min before the start of behavioural observation.

Enzyme immunoassay of histamine (see Appendix S1[1])

Western blot analysis (see Appendix S1[1])

Reverse transcription-PCR (see Appendix S1[1])

Statistical analysis

The data are presented as means ± standard error of the mean (SEM). Statistical significance was evaluated using the Student's *t*-test, two-way analysis of variance (ANOVA), or repeated measures two-way ANOVA followed by a *post hoc* Holm-Šidák test. $p < 0.05$ was considered significant. Statistical analyses were performed using Sigmaplot™ graphing and statistical software (version 11.2; Systat Software, Inc., San Jose, CA, USA).

RESULTS

Induction of dermatitis and pruritus

Although we have recently found that a single topical application of 1% and 10% sodium laurate to the back skin increases hind-paw scratching in Slc:ICR mice 2 h after application (7), a single topical application of 10% SDS did not significantly increase hind-paw scratching in Slc:ICR mice 2 h after application; scratching bouts per hour were 30 ± 7 and 43 ± 7 ($n = 8$ each) in the vehicle- and SDS-treated groups, respectively. In contrast to the acute effect, daily application of 0.1–10% SDS for 4 days increased hind-paw scratching in a concentration-dependent manner; the effect of 10% SDS was marked and highly significant (Fig. 1A). Thus, 10% SDS was used in the subsequent experiments. One day following application, scratching bouts were slightly but significantly increased, although skin lesion score, SC hydration, TEWL, and skin surface pH were not significantly changed (Fig. 1B–F). Repeated application of 10% SDS increased hind-paw scratching, caused dermatitis, decreased SC hydration, increased TEWL, and increased skin surface pH (Fig. 1B–F). All examined parameters were time-dependently enhanced during the 4-day treatment, and all changes were statistically significant 2 days after the start of SDS treatment (Fig. 1B–F). On the other hand, another neutral anionic surfactant, 10% *N*-lauroylsarcosine sodium salt, did not affect cutaneous parameters (dermatitis score, SC hydration, TEWL, and skin surface pH) and did not increase scratching even after repeated topical application in Slc:ICR mice (Fig. 1 B–F).

Effects of naloxone and terfenadine

To confirm that SDS-induced hind-paw scratching is an itch-associated behaviour, we examined the effect of the opioid receptor antagonist naloxone. Subcutaneous administration of naloxone (1 mg/kg) significantly suppressed hind-paw scratching induced by a 4-day topical application of SDS in Slc:ICR mice (Fig. 2).

Next, we examined the involvement of histamine in SDS-induced hind-paw scratching. Oral administration of the peripherally acting H_1 histamine receptor antagonist terfenadine (30 mg/kg) significantly suppressed scratching behaviour induced by a 4-day topical application of SDS in Slc:ICR mice (Fig. 2).

Effects of mast cell deficiency

Mast cell deficient WBB6F1-*W/W*^{v} mice and their normal littermates (WBB6F1-+/+) received topical applications of 10% SDS or vehicle to the skin once daily for 4 days. Repeated SDS treatment gradually increased hind-paw scratching in WBB6F1-*W/W*^{v} and WBB6F1-+/+ mice with a similar time course (Fig. 3A). Repeated SDS treatment did not affect the histamine content in the dermis of the treated skin in WBB6F1-+/+ mice (Fig. 3B). The histamine content in the dermis of the WBB6F1-*W/W*^{v} mice was approximately 1/100 that of the WBB6F1-+/+ mice and was not increased by repeated SDS treatment (Fig. 3B).

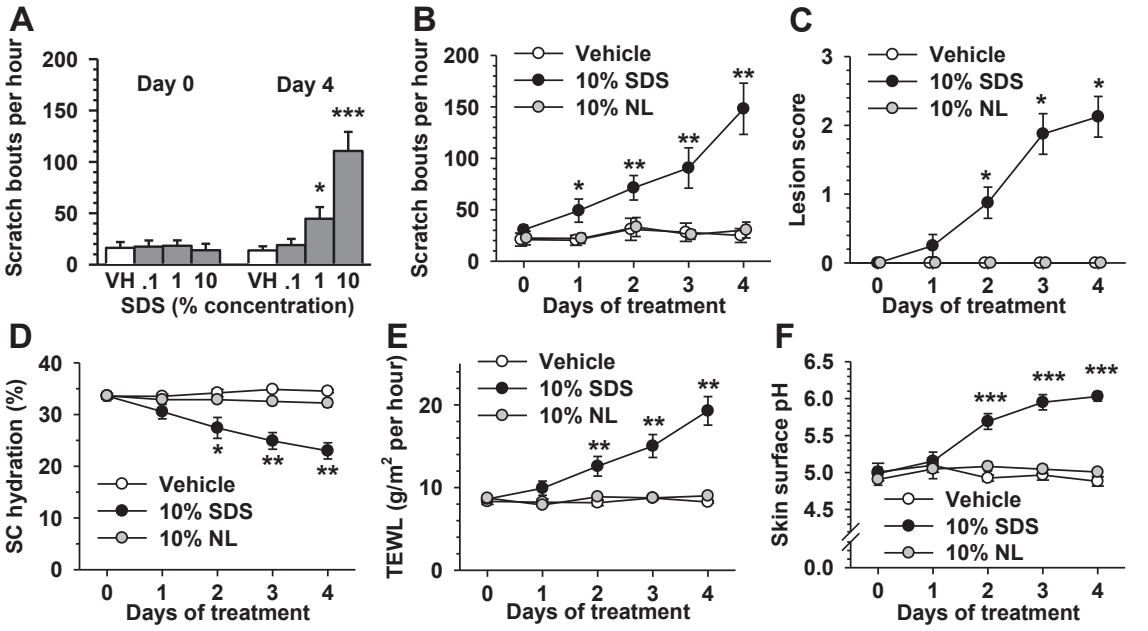

Fig. 1. Scratching behaviour, dermatitis, stratum corneum (SC) hydration, transepidermal water loss (TEWL), and skin surface pH in mice receiving repeated topical application of sodium dodecyl sulphate (SDS) and *N*-lauroylsarcosine sodium salt (NL). Slc:ICR mice received topical application of SDS, NL, or vehicle to the skin once daily. (A) Concentration-dependent increase of hind-paw scratching. Mice were given topical application of 0.1%, 1%, or 10% SDS for 4 days. (B–F) Time-dependent effects of 10% SDS and 10% NL on hind-paw scratching (B), skin lesions (C), SC hydration (D), TEWL (E), and skin surface pH (F). Values represent the mean ± SEM ($n = 6$ or 8). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. vehicle (Holm-Šidák test).

Histamine content in the epidermis

Although SDS-induced scratching was inhibited by terfenadine, it was not affected by mast cell deficiency, suggesting that histamine in mast cells does not play a key role in SDS treatment-induced scratching. We therefore investigated the effect of a 4-day application of SDS on histamine production in the epidermis. The content of histamine in the epidermis (0.067 ± 0.020 ng/mg wet tissue, $n = 3$) was as low as 3‰ of that in the dermis (26.2 ± 3.6 ng/mg wet tissue, $n = 3$) in normal Slc:ICR mice. Repeated application of SDS significantly increased the histamine content of the epidermis by 19-fold (Fig. 4A). The same treatment significantly increased the content of epidermal histamine in WBB6F1-*W/W*^{v} mice by 41-fold; histamine content was 0.0067 ± 0.0031 and 0.273 ± 0.065 ng/mg wet tissue in vehicle- and SDS-treated mice ($n = 4$ each), respectively.

Histamine and L*-histidine decarboxylase in the epidermis*

L-Histidine decarboxylase (HDC) is a key enzyme for the endogenous production of histamine. HDC is present as a low-active 74 kDa precursor protein and in an active 53-kDa form (15). Repeated SDS application significantly increased the expression levels of 74 and 53 kDa HDCs by 3.6- and 10.5-fold, respectively, in the treated epidermis (Fig. 4B). Unexpectedly, the level of β-actin was markedly decreased by SDS treatment (Fig. 4B);

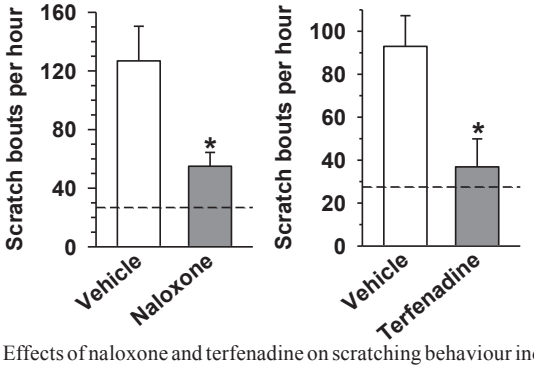

Fig. 2. Effects of naloxone and terfenadine on scratching behaviour induced by repeated topical application of sodium dodecyl sulphate (SDS). Slc:ICR mice received a topical application of 10% SDS to the skin once daily for 4 days. Naloxone (1 mg/kg, subcutaneous) and terfenadine (30 mg/kg, oral) were administered 15 and 30 min, respectively, before the start of behavioural observations. Broken lines denote the number of scratching bouts in the water-treated group. Values represent the mean ± SEM ($n = 8$). *$p < 0.05$ (Student's *t*-test).

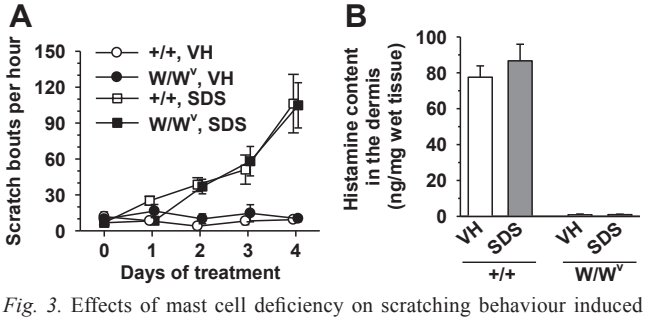

Fig. 3. Effects of mast cell deficiency on scratching behaviour induced by repeated topical application of sodium dodecyl sulphate (SDS) and the histamine content in the dermis. Mast cell deficient mice (WBB6F1-*W/W*^{v}) and their normal littermates (WBB6F1-+/+) received topical application of 10% SDS or vehicle (VH, distilled water) to the skin once daily for 4 days. (A) Time-dependent change in scratching behaviour. Values represent the mean ± SEM ($n = 6$ or 7). (B) The histamine content in the dermis. Values represent the mean ± SEM ($n = 4$).

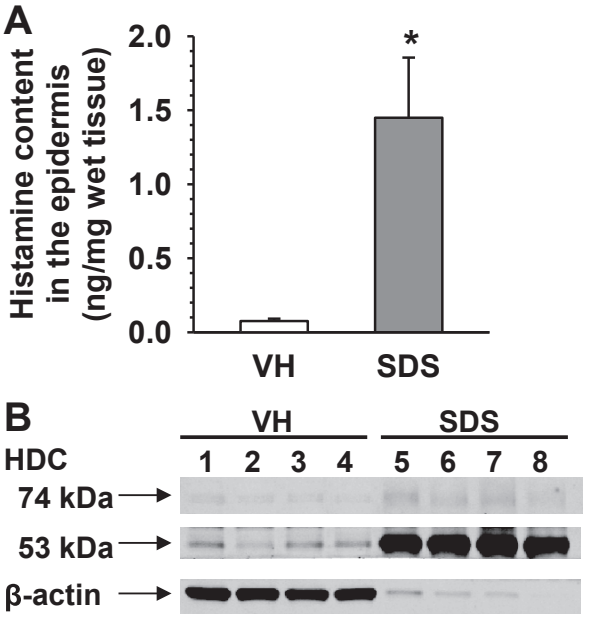

Fig. 4. Effects of repeated topical application of sodium dodecyl sulphate (SDS) on the histamine content and L-histidine decarboxylase (HDC) level in the epidermis. Slc:ICR mice received topical application of 10% SDS or vehicle (VH) to the skin once daily for 4 days. (A) Histamine content in the epidermis. (B) Western blotting for 53 and 74 kDa HDCs in the epidermis. Lanes 1–4, VH; lanes 5–8, 10% SDS. Values are presented as the mean ± SEM ($n = 4$). *$p < 0.05$ (Student's t-test).

the level of glyceraldehyde 3-phosphate dehydrogenase, another house-keeping gene, was also decreased (data not shown). Therefore, the HDC expression level was not quantified.

To examine the effects of SDS treatment on HDC gene expression, we determined HDC mRNA levels in the epidermis by reverse transcription-PCR. HDC mRNA levels in the epidermis gradually increased during the 4-day SDS treatment and changes became statistically significant starting 2 days after the start of treatment (Fig. 5).

DISCUSSION

SDS exposure is a standard method of inducing dermatitis and dryness in animal skin, but its effectiveness is dependent on the duration and frequency of SDS exposure (9). In the present study, the daily topical application of 50 µl of 10% SDS gradually increased dermatitis, reduced SC hydration, increased TEWL, and increased skin surface pH over a 4-day treatment period. The degree of decreased SC hydration and increased TEWL was milder in this study than in another report, in which 500 µl of 10% SDS in 70% ethanol was topically applied once daily for 4 days in hairless HR-1 mice (11). SDS application in our study gradually increased hind-paw scratching, as examined 22–24 h after each SDS application, which may therefore be due to changes in cutaneous conditions rather than surfactant irritation. SDS-induced scratching was inhibited by naloxone. Opioid receptor antagonists, including naloxone, inhibit itching and scratching in patients with various pruritic diseases such as atopic dermatitis and chronic urticaria (16) and experimentally induced itch in humans (17). In animals, naloxone inhibits hind-paw scratching elicited by intradermal injection of pruritogens (18, 19) and spontaneous scratching in murine models of pathological pruritus (20, 21). With these findings taken into account, the present results suggest that hind-paw scratching in the SDS-treated skin is an itch-related response.

Repeated SDS exposure-induced scratching was markedly and significantly suppressed by terfenadine at the oral dose of 30 mg/kg. Terfenadine at this dose has been shown to inhibit scratching and plasma extravasation induced by an intradermal injection of histamine (22, 23) but not scratching induced by other pruritogens such as sphingosylphosphorylcholine and nociceptin (24, 25). With this taken into account, the above-mentioned results suggest that the block of histamine action by terfenadine in the skin is responsible for the suppression of SDS-induced scratching. Histamine is present mainly in mast cells in the dermis (7, 26, 27). Histamine content in the dermis was almost abolished by mast cell deficiency. Repeated SDS exposure increased hind-paw scratching to the same degree in mast cell-deficient

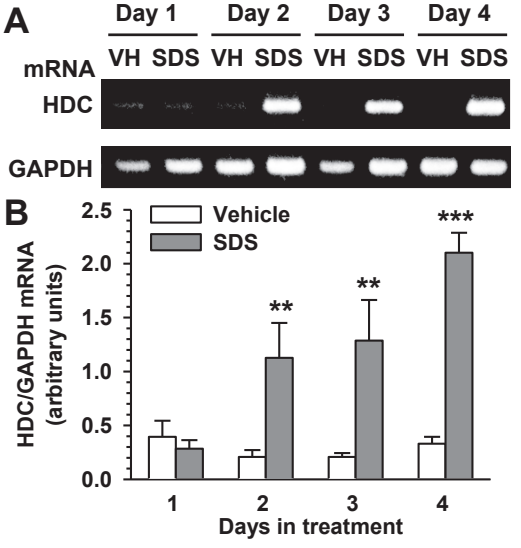

Fig. 5. Time-dependent changes in L-histidine decarboxylase (HDC) mRNA expression in the epidermis of the sodium dodecyl sulphate (SDS) treated skin. Slc:ICR mice received topical application of 10% SDS or vehicle (VH, distilled water) to the skin once daily for 4 days. The skin was isolated 22–24 h after the last SDS or VH application. (A) Typical examples of the bands of HDC and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNAs in the epidermis. (B) Semi-quantitative analysis of HDC mRNA levels in the epidermis. The expression level was normalised to the level of GAPDH mRNA. Values are presented as the mean ± SEM ($n = 3$–5). **$p < 0.01$, ***$p < 0.001$ vs. VH on each day (Holm-Šidák test).

mice and their normal littermates. In addition, repeated SDS exposure did not increase histamine content in the dermis of mast cell deficient and normal mice. These results, taken together, suggest that histamine in mast cells and other histamine-containing dermal cells, such as macrophages (28), is not responsible for the repeated SDS application-induced scratching.

Histamine is present in the epidermis although the level is very low and a single topical application of another surfactant, sodium laurate, transiently increases epidermal histamine content (7). Therefore, we examined the effects of repeated SDS exposure on epidermal histamine content and on the expression of the histamine-producing enzyme HDC in the epidermis. Repeated topical application of SDS markedly increased histamine content in the epidermis. The same treatment also markedly increased the expression level of HDC mRNA. This increase was obvious from 2 days after the start of SDS treatment, the time course of which roughly corresponded to the time course of increase in scratching. Additionally, repeated SDS treatment significantly increased protein expression levels of 74 and 53 kDa HDCs in the epidermis. These findings suggest that repeated SDS treatment increases HDC protein synthesis. In mast cells, HDC is translated as a 74 kDa precursor protein and is post-translationally cleaved to a 53–55 kDa species (15). The 74 kDa HDC exhibits low enzyme activity, and thus histamine is synthesised mainly by the 53 kDa HDC and then stored in granules (15). The amount of 53 kDa HDC present after repeated SDS treatment was 2.9-fold higher than that of 74 kDa HDC. These findings suggest that the increased histamine content is due to an increase of HDC protein synthesis and post-translation processing from 74 to 53 kDa HDC that results in increased epidermal histamine production.

The present results did not reveal the type of epidermal cells on which SDS acted. However, keratinocytes that account for about 95% of the cells of the epidermis express HDC and contain histamine (7, 29), and administration of sodium laurate to cultured epidermal keratinocytes increases the cleavage process from 74 to 53 kDa HDC and histamine production (7). Therefore, it is suggested that topically applied SDS increases HDC expression and histamine production in the epidermal keratinocytes. Although histamine is stored in granules after it is synthesised by HDC in mast cells (15), it is spontaneously released after biosynthesis in macrophages because of their lack of histamine-storing granules (15, 30). Similarly, increased histamine synthesis along with a lack of histamine-storing granules in epidermal keratinocytes may result in an increase in the spontaneous release of histamine. Thus, it is suggested that increased production (and content) of histamine in epidermal keratinocytes is responsible for the histamine-mediated scratching observed after repeated SDS exposure. Histamine is synthesised from histidine by HDC. To our knowledge, there have been no previous reports on the content of histidine in keratinocytes. However, keratohyalin granules contain histidine (31), keratinocytes contain the histidine-rich protein filaggrin, which is degraded into amino acids including histidine, and there is a substantial amount of histidine in the SC (32). Therefore, a sufficient concentration of histidine may be present in keratinocytes.

The histamine content of the epidermis in WBB6F1-*W/W^v* mice was about 1/5 of that in Slc:ICR mice after repeated SDS treatment, while scratching bouts were almost comparable between these strains. This may not be due to strain differences in innate histamine sensitivity, because scratching bouts following intradermal histamine injection is much lower in WBB6F1-*W/W^v* mice than in Slc:ICR mice (33). In the present experiments, scratching bouts after repeated SDS treatment were similar between WBB6F1-*W/W^v* and WBB6F1-+/+ mice. In addition, scratching bouts following intradermal histamine injection is similar between these mice (33). Therefore, mast cell deficiency may not affect histamine sensitivity. In our preliminary experiments, repeated SDS treatment markedly increased nerve fibres in the epidermis, which might affect histamine sensitivity. Although further experiments are needed, SDS-induced changes other than histamine production might alter histamine sensitivity to varying degree in Slc:ICR and WBB6F1-*W/W^v* mice.

Although the detailed mechanisms of increased HDC expression in the epidermis remain unclear, it has been recently reported that activation of Toll-like receptor (TLR) induces HDC expression (34). Ten human and 12 murine TLRs have been identified (35): TLR1–TLR10 in humans, and TLR1–TLR9, TLR11, TLR12 and TLR13 in mice (the homologue of TLR10 being a pseudogene). Intravenous administration of TLR2/6-, TLR3-, and TLR4 agonists induced HDC expression in the liver, spleen, and lungs (34). Skin keratinocytes express TLR1–6 and 9 (36–38). Although the mammalian TLRs are traditionally known to sense pathogen-associated molecular patterns, such as bacterial lipopolysaccharide, lipopeptides, and flagelline, recent studies have demonstrated that they also detect host-derived molecules, such as hyaluronic acid (39, 40), heparin sulphate (41), fibrinogen (42), surfactant protein-A (43), high-mobility group box 1 (44), β-defensin (45), heat-shock proteins (46, 47), and messenger RNA (48). These endogenous ligands for TLRs can be expressed or released in response to tissue damage. Considering that skin keratinocytes express TLRs, these findings raise the possibility that the increase of HDC expression in the epidermis is due to the expression or release of endogenous ligands for TLRs resulting from repeated SDS exposure-induced inflammatory damage.

Repeated SDS application increased skin surface pH from 5.0 to 6.0. The time course for this increase roughly corresponded to the time course of increase in scratching. We have recently demonstrated that a single topical app-

lication of the anionic surfactant sodium laurate increases scratching transiently (2–3 h after application) with an elevation of skin surface pH to 6.0 (7). In contrast, both single and repeated topical applications of *N*-lauroylsarcosine sodium salt did not increase skin surface pH and scratching (7; present results). These findings suggest that increased pH is an important factor in the pruritogenic activity of topically applied surfactants. A single topical application of sodium laurate increases post-translation processing from the 74 to the 53 kDa form of HDC in the epidermis (7). Interestingly, repeated SDS application also increased post-translation processing of HDC in the epidermis. These findings suggest the possibility that increased pH plays a role in the mechanism of the post-translation processing of HDC. Although details of the mechanisms of HDC processing remain unclear, benzamidine-sensitive proteinase has been reported to be involved in HDC processing (49). Benzamidine-sensitive proteinase is activated at an alkaline pH (pH 8–9) (49, 50). The pH values of the SDS and *N*-lauroylsarcosine sodium salt solutions were 6.5 and 7.7, respectively. An increase in skin surface pH results in the destruction of the barrier function of the SC (51), and the topical application of sodium hydroxide solution increases the subcutaneous pH from 7 to higher than 10 (52, 53). In a previous study, we showed that scratching bouts were not increased after the application of sodium hydroxide solution. On the basis of these findings, it is suggested that HDC processing is not increased by the elevation of extracellular pH. Although we did not determine the duration of intracellular pH increase, repeated SDS treatment might increase HDC processing through an elevation of intracellular pH due to both its anionic and surface activities.

In conclusion, we demonstrated that repeated SDS application to the murine skin induced itch-associated scratching behaviour through an increase of histamine production in the epidermis, resulting from an increase of HDC protein synthesis and post-translation processing from 74 to 53 kDa HDC.

The authors declare no conflict of interest.

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