

Stratum corneum cytokines and skin irritation response to sodium lauryl sulfate

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Little is known about cytokines involved in chronic irritant contact dermatitis. Individual cytokine profiles might explain at least part of the differences in the individual response to irritation. Our objective was to investigate the relation between baseline stratum corneum (SC) cytokine levels and the skin response to a single and a repeated irritation test. This study also aimed to determine changes in SC cytokine levels after repeated irritation. Transepidermal water loss (TEWL) and erythema were measured in 20 volunteers after single 24-hr exposure to 1% sodium lauryl sulfate (SLS), and during and after repeated exposure to 0.1% SLS over a 3-week period. SC cytokine levels were measured from an unexposed skin site and from the repeatedly exposed site. Interleukin (IL)-1 α decreased by 30% after repeated exposure, while IL-1RA increased 10-fold and IL-8 increased fourfold. Baseline IL-1RA and IL-8 values were predictors of TEWL and erythema after single exposure ($r = 0.55$ – 0.61). 6 subjects showed barrier recovery during repeated exposure. Baseline IL-1RA and IL-8 levels are likely to be indicators of higher skin irritability after single exposure to SLS. Barrier repair in some of the subjects might explain the lack of agreement between the TEWL response after single and repeated irritation.

Key words: barrier repair; cytokines; inflammation; irritant contact dermatitis; sodium lauryl sulfate; stratum corneum; tape stripping. © Blackwell Munksgaard, 2006.

Accepted for publication 13 February 2006

Chronic irritant contact dermatitis (ICD) occurs frequently in several occupations, e.g. hairdressing (1–3), nursing (2, 4) and metalworking (5–7). For example, in studies of junior hairdressers, about 35% developed ICD during their first year (1, 8). While acute ICD occurs after a single exposure to a strong irritant, repetitive irritation of the skin with a mild irritant can cause chronic ICD (9). The mechanism of the development of chronic ICD and the factors that predispose individuals to this skin disease are not completely understood.

Screening of individuals at risk is an important activity in occupational medicine, and such screening must be based on the knowledge of certain predictive characteristics. It was thought that the results of short exposure to the irritant sodium lauryl sulfate (SLS) might provide a predictive indicator of ICD. However, investigations have shown that an individual's reaction to a single SLS irritation fails to predict the skin reaction to repeated irritation (10–12).

Understanding the role of cytokines in skin irritation might help in the identification of

individual susceptibility factors for chronic ICD. Cytokines play an important role in inflammatory processes occurring in the skin (13). After skin contact, SLS impairs the stratum corneum (SC) barrier (14–16) and exerts a direct toxic effect on the keratinocytes (17, 18). In response to these changes, preformed cytokine interleukin-1 α (IL-1 α) is released from the SC and keratinocytes as the first step in the inflammatory cascade. IL-1 α stimulates other keratinocytes and fibroblasts to produce and release more IL-1 α and other primary pro-inflammatory cytokines IL-1 β , IL-6, IL-8 and tumour necrosis factor- α (TNF- α) (13, 19–22). The induced cytokine cascade results in an inflammatory reaction with vasodilatation in the dermis and cellular infiltrate in the epidermis (20, 23, 24). However, to counteract these inflammatory processes, keratinocytes also produce anti-inflammatory cytokines. IL-1 receptor antagonist (IL-1RA) is a cytokine that blocks IL-1 activity by competitive binding to the IL-1 receptor without triggering a signal cascade (13, 21). IL-10 is another example of an anti-inflammatory

cytokine produced by keratinocytes (13). In view of the important role of cytokines as inflammatory mediators, one may speculate that interindividual variations in the level of cytokine present or produced in the skin will contribute to variations in the intensity of an irritation reaction (25).

Several researchers have studied the cytokine response in the skin *in vivo* after a single irritant challenge, mostly with SLS (26–30). However, to our knowledge, no human *in vivo* data are available on the cytokines involved in chronic ICD. The cytokine pattern in chronic ICD is likely to differ from the acute pattern, as data on another inflammatory skin disease, atopic dermatitis, show that the mechanism and the involved cytokines of an acute dermatitis differ from those of a chronic dermatitis (31). Several methods are used for skin cytokine sampling in humans, e.g. measurement of cytokines in punch biopsies (26, 27, 30), skin-derived lymph (28, 32) or suction blister fluids (29, 32, 33). These techniques are, however, invasive. A non-invasive method based on tape stripping that can be used for measurement of a number of cytokines in the SC has been proposed (34, 35).

The objective of the present study was to investigate the relation between baseline SC cytokine levels and the skin irritation response to a single 24-hr SLS exposure and after repeated exposure over a 3-week period, in search for a predictive parameter for chronic ICD. This study also aimed to determine changes in SC cytokine levels in skin repeatedly exposed to SLS.

We performed a single 24-hr 1% SLS irritation test and a repeated 3-week irritation test (0.1% SLS) on healthy volunteers. To assess the skin reaction during and after these exposures, we used transepidermal water loss (TEWL) as an effect parameter for the skin barrier function and erythema for the extent of skin inflammation. 4 days after the last exposure, the SC cytokine levels (IL-1 α , IL-1RA, IL-2, IL-6, IL-8, IL-10 and TNF- α) at the site subjected to repeated exposure and at an unexposed control site (to give the baseline values) were assessed by means of SC tape stripping. The rate of penetration of SLS into the SC was also determined in this study (36).

Subjects and Methods

Study population

20 healthy, non-smoking volunteers, with no visible skin abnormalities and no history of skin disease, participated in the study [13 women aged 24 ± 3 years (mean $\pm$ SD) and 7 men aged 25 ± 8 years]. The study was approved by

the Ethics Committee of the Academic Medical Center, Amsterdam, and all subjects gave their written, informed consent. The subjects were not allowed to (i) use soap or moisturizers on their forearms during the investigation, (ii) sunbathe or use a tanning bed 2 months prior to, and during, the investigation and (iii) use corticosteroids 2 months before or during the investigation. All participants completed the Erlanger Atopy Questionnaire (37) in the presence of the investigator. Subjects with an atopy score calculated from the answers to this questionnaire which is ≥ 10 are considered to be skin atopic.

Single 24-hr exposure to SLS

The dominant mid-volar forearm was exposed over a 24-hr period to a 1% w/v SLS solution (200 μ l, 99% purity, Fluka, Buchs, Switzerland), using a patch test chamber (Finn chambers[®] of 18-mm diameter and Filter Paper Discs, Epitest Ltd Oy, Tuusula, Finland). Before application and 24 hr after patch removal, TEWL and erythema were measured at the exposed site and at a control site on the volar forearm. TEWL was measured using an evaporimeter (VapoMeter SWL2g, Delfin Technologies Ltd, Kuopio, Finland). Nuutinen et al. describe this measurement device in detail (38). For at least 20 min prior to the measurements, the volunteers rested with their sleeves rolled up in the examination room, where the temperature was 20–22°C and the relative humidity ranged from 50% to 60%. The erythema index (skin redness) was measured using an erythema meter (DermaSpectrometer; Cortex Technology, Hadsund, Denmark) as described by Clarys et al. (39).

Repeated 3-week exposure to SLS

2 sites on the non-dominant mid-volar forearm were exposed to a 0.1% SLS solution (200 μ l) for 6 hr a day, 4 days a week, for 3 weeks using the same patches as for the 24-hr SLS exposure. TEWL and erythema were measured at the exposed sites and at a control site before, during and after the exposure period (on days 0, 3, 7, 10, 14, 17, 21, 23 and 28). On days when patches were applied, the measurements were performed prior to patch application.

Stratum corneum tape stripping and extraction

Tape stripping was performed 4 days after the final exposure to SLS (day 21) to ensure that the observed pattern of SC cytokines originates from a repeated skin irritation and not from an acute irritation reaction, which might be the case

if the SC cytokine pattern were measured 1 day after the final 6-hr exposure to SLS in the 3-week test. The SC was removed from one of the repeatedly exposed sites and from the unexposed control site using 20×25 -mm pieces of polypropylene tape with a water-soluble adhesive (PPCBT-K7, Sentega Etiketten BV, Utrecht, the Netherlands). Templates of Scanpor[®] tape (Norgeplaster, Vennesla, Norway) were fixed to the skin around each application spot to limit the tape stripping area to a circle of 18-mm diameter. Pieces of the polypropylene tape were successively applied to the sites and homogeneously pressed on to the skin by moving a 1.0-kg stainless steel roller (10) to and fro 10 times. The tapes were then removed at an angle of 170° with the skin. The sites were stripped in multiple directions until the SC was totally removed, as indicated by the shininess and redness of the surface and a TEWL of $>100 \text{ g/m}^2/\text{hr}$. The tape stripping of the 2 sites was completed in 15 min. Each tape strip was collected in a 2-ml polypropylene tube (Fisher Emergo, Landsmeer, the Netherlands) and stored at -80°C .

To extract the SC, 1.5 ml of phosphate-buffered saline (Merck, Darmstadt, Germany) with 0.005% Tween-20 (Sigma-Aldrich, Zwijndrecht, the Netherlands) was added to each tube and the tubes were left on ice for 30 min. The SC was subsequently extracted using an ultrasound sonifier equipped with a probe (Salm & Kipp, Breukelen, the Netherlands) for 15 min in ice water. The extract was centrifuged (1 min, 15 000 g) and supernatant aliquots of 225 μl were re-frozen at -80°C until required for further analysis.

Cytokine and protein assay

3 times 4 consecutive tapes were selected from the total series of strips from each tape-stripped site: 4 strips from the superficial third, 4 from the middle third and 4 from the deepest third part of the SC. The SC extracts from the selected strips at each SC position were analysed for the cytokines IL-1 α , IL-1RA, IL-2, IL-6, IL-8, IL-10 and TNF- α using specific enzyme-linked immunosorbent assay (ELISA) kits (Human CytoSets, Biosource International, Camarillo, CA, USA). 2 different cytokines were determined in the SC extract of each strip (e.g. IL-1 α and IL-1RA were measured in the same strip). The amount of cytokines on each strip was normalized to the soluble protein content of the strips as determined with the aid of the Micro BCA protein assay kit (Pierce, Rockford, IL, USA), using the bovine serum albumin supplied as standard. Standards and samples were pipetted into a 96-well

plate and analysed following the instructions provided with the kits. The data for the 3 superficial, middle and bottom strips at each site were pooled to obtain 1 average value for each cytokine.

Statistics

All data are given as mean $\pm$ SD, unless otherwise indicated. Statistical analyses were performed using Student's *t*-test for paired samples or two samples, Pearson's correlation coefficient and one-way analysis of variance (ANOVA). If appropriate, normal distributions were obtained by log-transformation of the data.

Results

TEWL and erythema response to single and repeated exposure

1 day after the single SLS exposure, the average TEWL had increased from 9.0 ± 3.0 (baseline) to $81.1 \pm 42.2 \text{ g/m}^2/\text{hr}$ and erythema from 7.8 ± 2.1 to 12.2 ± 3.2 arbitrary units (AU).

2 subjects had to withdraw from the repeated SLS exposure after 1 week because of strong erythema reactions. Both subjects were non-atopics according to their Erlanger atopy score. Figure 1 shows the changes in TEWL (ΔTEWL) and erythema ($\Delta\text{erythema}$) compared with baseline values during the repeated SLS exposure. TEWL was observed to increase during the first week, with a partial recovery during the non-exposure days. The rise in TEWL was even stronger in week 2, again being followed by partial recovery. Interestingly, the increase in TEWL in the third week was less than that in the second week (day 17 versus day 10; $P = 0.06$, 2-sided). In contrast to TEWL, erythema increased continuously during the first 2 weeks, even during days with no exposure, and flattened out in the third week.

Relation between TEWL and erythema response to single and repeated exposure

During the first week of the repeated irritation, a positive correlation was found between the extent of the skin responses to single and repeated exposure, both for ΔTEWL (day 3, $r = 0.60$, $P = 0.003$) and for $\Delta\text{erythema}$ (day 3, $r = 0.66$, $P < 0.001$). During the second week (data not shown) and the third week, a positive correlation between the responses to single and repeated exposure was found for $\Delta\text{erythema}$ (Fig. 2a, day 17, $r = 0.72$, $P < 0.001$), but not for ΔTEWL (Fig. 2b, day 17, $r = 0.06$).

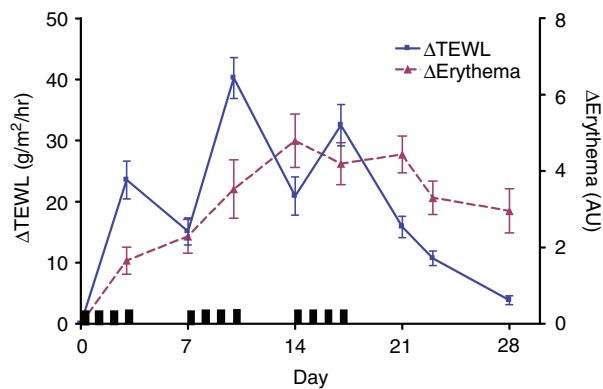


Fig. 1. Change in TEWL (Δ TEWL) and erythema (Δ erythema) during repeated exposure to SLS ($n = 18$). Data are expressed as mean $\pm$ SEM. The black blocks along the time axis indicate the exposure days. SLS, sodium lauryl sulfate; TEWL, transepidermal water loss.

Differences in TEWL response to repeated SLS exposure

As mentioned above, the average Δ TEWL in the third week of repeated exposure to SLS was lower than in the second week, suggesting repair to the irritation. This pattern was however not seen in all subjects. 5 subjects showed a high Δ TEWL (>36 g/m²/hr) in both the second and the third week. A second group of 6 subjects showed a decrease in Δ TEWL, indicating repair of the water barrier, during the third week (Δ TEWL <30 g/m²/hr) compared to the second week. A third group ($n = 5$) showed only a small effect on the skin water barrier during the entire exposure period (Δ TEWL <30 g/m²/hr), while 2 other subjects showed a delayed response, with a small effect on the skin water barrier on day 10 but an increase in Δ TEWL on day 17.

Subjects with a high baseline TEWL value tended to have a higher Δ TEWL at the end of

repeated exposure to SLS ($r = 0.44$; $P = 0.04$, 1-sided).

Effect of atopy on TEWL and erythema response

The subjects' Erlangen Atopy Score was 7.9 ± 3.9 (mean $\pm$ SD) and ranged from 3 to 16; the maximum possible score is 34. 6 subjects scored ≥ 10 points, which is considered as having atopy (37). Baseline TEWL did not clearly differ between subjects with and without atopy (9.2 ± 3.9 versus 9.0 ± 2.7 , respectively; $P = 0.9$). After single exposure to SLS, TEWL increased by 92.5 ± 44.9 g/m²/hr in the atopy group, compared to 62.6 ± 36.2 g/m²/hr in non-atopics ($P = 0.07$, 1-sided). The increase in erythema for these groups was 5.9 ± 2.5 and 3.4 ± 2.6 AU, respectively ($P = 0.03$, 1-sided). The value of Δ TEWL after repeated exposure did not differ significantly between atopics and non-atopics on any measurement day. On days 10, 14 and 17, Δ erythema was higher in the atopy group than in the other group ($P < 0.05$, 1-sided, data not shown).

SC cytokine levels in unexposed and repeatedly exposed skin

A total of 28 ± 4 tapes were required for complete removal of SC from the site repeatedly exposed to SLS, as compared with 26 ± 5 tapes at the control site. Figure 3 shows the amount of cytokines (IL-1 α , IL-1RA and IL-8) normalized for the soluble protein content and the ratio IL-1RA/IL-1 α in SC obtained from the control site and from the site repeatedly exposed to SLS (measured on day 21). The following cytokines were not detected in any SC samples (the LOD – limit

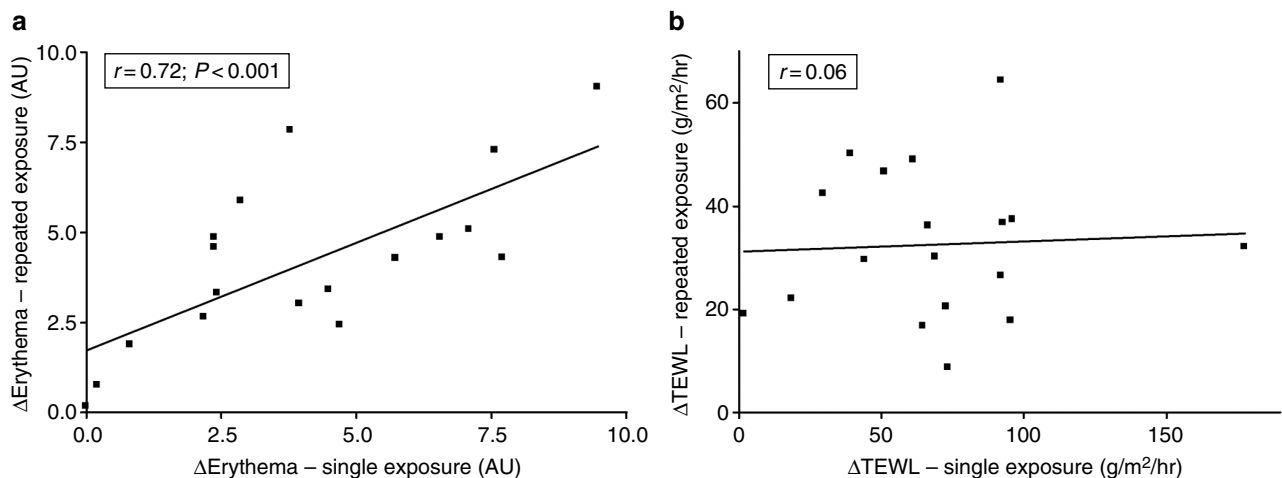


Fig. 2. Relation between (a) the increases in erythema and (b) the increases in TEWL after single and repeated (day 17) exposure to SLS. SLS, sodium lauryl sulfate; TEWL, transepidermal water loss.

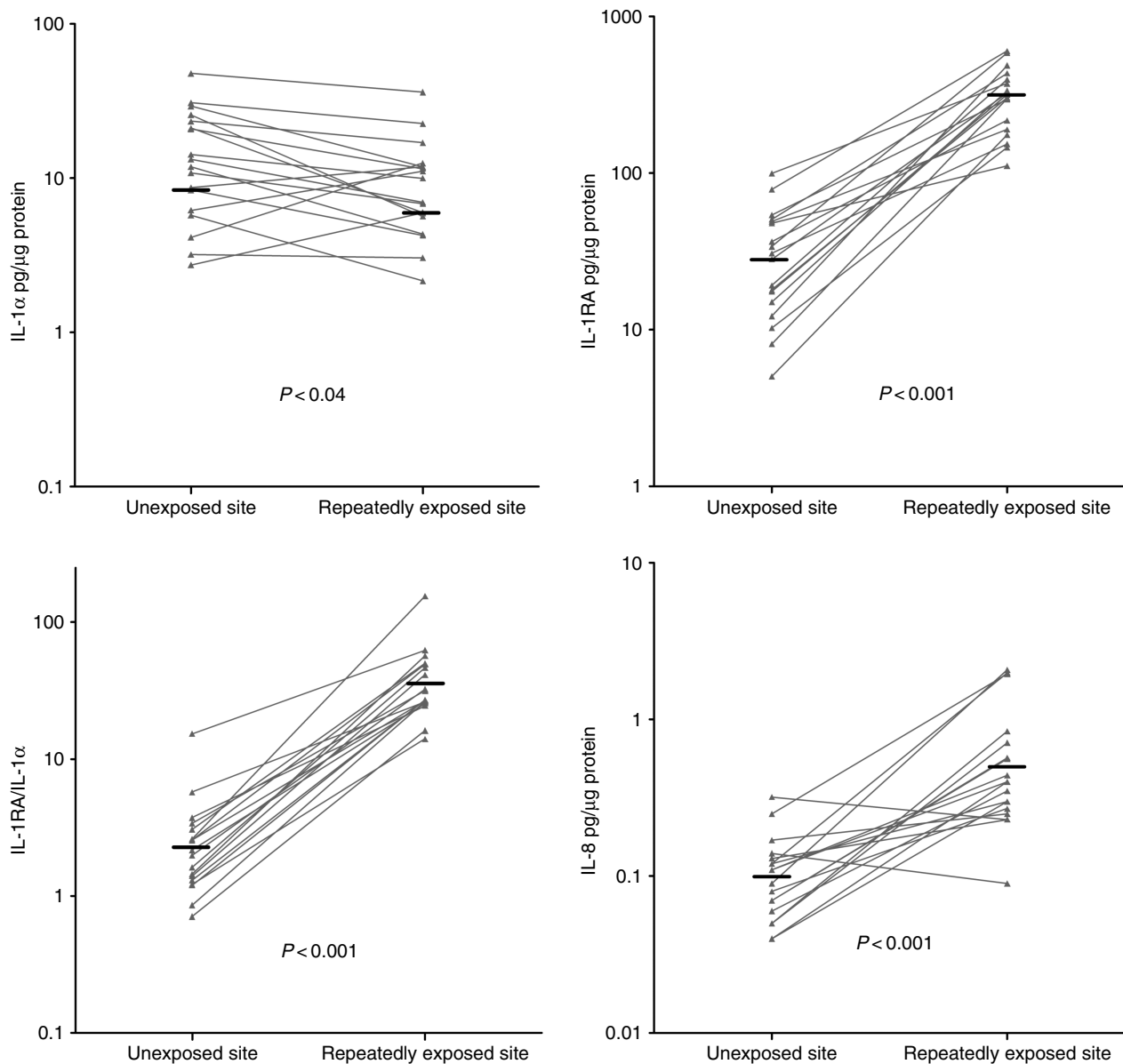


Fig. 3. The amount of cytokines (IL-1 α , IL-1RA, ratio IL-1RA/IL-1 α and IL-8) in SC tape strips normalized to soluble protein content for each subject ($n = 18$) from the unexposed site and the site repeatedly exposed to SLS; — indicates the geometric mean, paired t -test on log-transformed data. SLS, sodium lauryl sulfate.

of detection – is given between brackets): IL-2 (30 pg/strip), IL-6 (6 pg/strip), IL-10 (8 pg/strip) and TNF- α (2 pg/strip). As can be seen from Fig. 3, considerable interindividual differences in cytokine levels were observed. A 30% decrease in IL-1 α ($P = 0.04$, 2-sided) and a 10-fold increase in IL-1RA ($P < 0.001$, 2-sided) were found in the SC after repeat exposure to SLS as compared to the control site. The IL-1RA/IL-1 α ratio for the site repeatedly exposed to SLS increased by a factor of 15 ($P < 0.001$, 2-sided) compared to the unexposed site. The amount of IL-8 showed a fourfold increase ($P < 0.001$, 2-sided). Only very small amounts of IL-8 were measured at the control site: 11 subjects had IL-

8-values just above the LOD of the assay (0.86 pg/strip). Samples with IL-8 values below the limit of detection were given a fictive value of 0.43 pg/strip ($= \frac{1}{2}$ LOD).

Baseline SC cytokine levels and TEWL and erythema response

A positive correlation was found between the IL-1RA content at the control site (baseline) and Δ TEWL and Δ erythema measured after single exposure to SLS (Table 1, $r = 0.61$ and $r = 0.60$; $P < 0.01$, respectively, 2-sided). Baseline IL-8 correlated with Δ TEWL ($r = 0.53$; $P = 0.02$, 2-sided) after the single exposure, but

Table 1. Pearson's correlation coefficients between (log) cytokine levels at the unexposed site and increase in TEWL and erythema after single or repeated exposure to SLS (day 17)

	Single SLS exposure (<i>n</i> = 20)		Repeated SLS exposure (<i>n</i> = 18)	
	ΔTEWL	Δerythema	ΔTEWL	Δerythema
IL-1α	0.12	0.07	−0.19	0.20
IL-1RA	0.61 ^a	0.60 ^a	−0.20	0.53 ^b
IL-1RA/IL-1α	0.56 ^b	0.59 ^a	−0.01	0.36
IL-8	0.53 ^b	0.36	0.05	0.11

IL, interleukin; SLS, sodium lauryl sulfate; TEWL, transepidermal water loss.

^a*P* < 0.01(2-sided).

^b*P* < 0.05.

not significantly with Δerythema (*r* = 0.36). When only subjects with an IL-8 value above the LOD were included (*n* = 11), the correlation between baseline IL-8 and ΔTEWL increased to *r* = 0.67 (*P* = 0.02, 2-sided) and that between baseline IL-8 and Δerythema to *r* = 0.55 (*P* = 0.08, 2-sided). No correlation was found between baseline SC cytokine levels and skin response after repeated exposure to SLS, except for IL-1RA which correlated with Δerythema measured on day 17 (last day of exposure, *r* = 0.53; *P* < 0.05, 2-sided). Furthermore, baseline cytokine levels did not differ between atopics and non-atopics.

Discussion

The single 24-hr exposure to 1% SLS led to an impaired skin water barrier and to skin inflammation in all subjects, although with considerable interindividual variation in the extent of these responses. The average increase in TEWL and erythema was 72 g/m²/hr and 4.4 AU, respectively, in agreement with other studies (40–42). Our study also confirmed that repeated exposure to 0.1% SLS over a period of 3 weeks caused barrier impairment and skin inflammation in all subjects, again with a considerable interindividual variation in response (10).

This study further confirms the finding that the impairment of the skin barrier, as determined by the change in TEWL, after a single exposure to SLS cannot be used to predict the change in TEWL after repeated exposure (10, 12). Koopman et al. (10) suggested that additional mechanisms that differ between subjects come into play after repeated exposure to SLS of sufficient duration, while these mechanisms are absent after a brief SLS exposure. In contrast to TEWL, erythema did show correlation between the scores after single and repeated SLS exposure (*r* = 0.72). A similar relationship was described by Koopman et al. (10) using a visually scored

erythema index. However, the association we found (*r* = 0.72) does not give sufficient predictive power to allow reliable screening of individuals for susceptibility to chronic ICD under occupational conditions.

The considerable interindividual variation was reflected not only in the intensity of the skin response after 3 weeks but also in the skin reaction pattern during the repeated exposure. We observed recovery of the skin water barrier during the third week of repeated exposure to SLS in 6 subjects. This phenomenon has already been reported by others. Widmer et al. and Heinemann et al., for example, found a slight decrease in TEWL during the third week of an SLS irritation test (0.5% SLS, 1-hr exposure for 5 days a week) (43, 44). Widmer et al. speculated that the improvement in the skin barrier might be due to hyperkeratosis of the epidermis induced by the irritation reaction. Hyperkeratosis causes thickening of the SC, leading to a better skin barrier (44). This hyperkeratotic reaction of the stratum corneum and epidermis to repeated SLS exposure, often described as the skin hardening phenomenon (45–47), might be an important factor in determining individual susceptibility to chronic irritation. Furthermore, it might be at least partly responsible for the lack of correlation between the changes in TEWL after single and repeated exposure to SLS. Further research is required in this field.

Not only SC thickness but also changes in the composition and structure of the lipid bilayer should be considered in trying to understand the mechanism of barrier repair. Heinemann recently demonstrated that the amount of ceramide 1 in the lipid bilayer was increased in subjects showing the hardening phenomenon (43). Ceramide 1 is important for the lipid organization in the SC that is required for an efficient skin barrier (48).

In our study, the IL-1RA/IL-1α ratio of 2.2 ± 2.1 in unexposed skin was almost identical with that reported by Terui et al. (2.2 ± 2.8) (35).

The increase in the IL-1RA/IL-1 α ratio due to irritation was primarily due to an increase in IL-1RA and to a lesser extent to a decrease in IL-1 α . The balance between IL-1RA and IL-1 α is important in the downregulation of the inflammatory response (49). An increase in IL-1RA/IL-1 α is commonly found in cutaneous inflammation processes and has been described in chronic disorders such as atopic dermatitis (35), psoriasis (35) and rosacea (49).

In addition to the increase in the IL-1RA/IL-1 α ratio, we found enhanced levels of IL-8 in the SC after repeated exposure. IL-8 is a pro-inflammatory chemokine, which is involved in skin irritation by attraction of polymorphonuclear neutrophils and lymphocytes to the site of inflammation (13, 21). It is known to be present intracellularly in the epidermis in normal healthy skin (50). We found quantifiable amounts of IL-8 in the SC of unexposed skin in 11 of our 20 subjects, in agreement with data reported by Perkins et al. (51).

The skin cytokine response has only been investigated with the aid of acute irritation tests so far. To the best of our knowledge, the present investigation is the first *in vivo* human study including determination of the cytokine levels after repeated skin irritation. The cytokine pattern we found in the SC is in accordance with that measured in punch biopsies determined in a parallel study on repeated SLS exposure (manuscript in preparation). Our study results reveal that levels of IL-1 α and IL-1RA after chronic irritation differ from those produced by a single irritation. Perkins et al. exposed subjects to 20% SLS for 1 hr and found an increase in IL-1 α and a decrease in the IL-1RA/IL-1 α ratio (51). Our study of repeated SLS exposure revealed effects opposed to this. On the other hand, a tendency for IL-8 levels to increase in response to SLS exposure was found both in the acute study of Perkins et al. (51) and in our study of repeated exposure effects.

One of our objectives was to study the relation between basal SC cytokine levels and individual skin reactions. Like other authors (34, 35, 51), we found cytokine levels in the SC of normal unexposed skin to vary widely between individuals. Interindividual differences in the cytokine levels were also considerable in our repeated SLS exposure tests. We found the baseline SC level of IL-1RA to be related to TEWL and erythema after a single exposure to SLS. Baseline IL-8 was related to increase in TEWL after single exposure. It was also related to an increase in erythema, although our study group only included 11 subjects with IL-8 levels above the detection limit of the assay. Higher baseline IL-1RA levels were also related to a higher increase in erythema after repeated

SLS exposure. These results suggest that subjects with higher baseline SC levels of IL-1RA and IL-8 have a stronger response to skin irritation. Further research is needed to elucidate the underlying mechanism. A more sensitive assay method is also needed to determine the amount of IL-8 in the SC in such further investigations.

Atopic constitution has been reported as a risk factor for chronic ICD (52). We did not preselect the subjects of the present study according to their atopy status. 6 of our 20 subjects were classified as atopics on the basis of their Erlangen Atopy Score. Our study showed that atopics are more susceptible to a single SLS exposure than non-atopics, as indicated by a stronger skin response (in terms of TEWL and erythema). This is in contrast to the results of Stolz et al. who found no clear relation between atopy score and TEWL increase after single SLS exposure (53). However, these authors measured TEWL only 1 hr after patch removal, when the occlusion effect of the patch might mask any effect of atopy on the skin barrier response (54). Atopics showed a higher inflammation reaction starting from the end of the second week in our repeated SLS exposure tests, but no difference in skin water barrier. This is in agreement with the results of a test involving repeated washing with SLS where more subjects with a visible eczema were found in the atopy group (55). In further agreement with our findings, these authors concluded that the atopy score had only limited value as a predictor of an increase in TEWL after repeated exposure.

In conclusion, the present study has shown that during repeated skin irritation, in some subjects, repair of the skin barrier occurred. This repair phenomenon might be responsible for the lack of agreement between the changes in TEWL after single and repeated irritant challenge. The erythema response to a single irritation appears to be a better predictor than TEWL. We further showed that baseline IL-1RA and IL-8 levels are indicators of skin irritability. Our study results contribute to an understanding of the factors that determine individual susceptibility to chronic ICD. A knowledge of the role interindividual variation in SC cytokine levels play in relation to a possible predisposition to occupational chronic ICD may help in the development of a screening test for pre-employment counselling.

Acknowledgement

The authors thank L. Dekker and S.W. Spiekstra for their technical assistance, E. Hull for his linguistic advice and Dr S. Gibbs and Prof S.M. John for their thoughtful review of and suggestions for this manuscript.

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