Neuronal Sensitization for Histamine-Induced Itch in Lesional Skin of Patients With Atopic Dermatitis

Akihiko Ikoma, MD; Roman Rukwied, PhD; Sonja Ständer, MD; Martin Steinhoff, MD, PhD; Yoshiki Miyachi MD, PhD; Martin Schmelz, MD, PhD

Objective: Lowered threshold of neurons (ie, neuronal sensitization) in atopic dermatitis was investigated by testing sensitivity to histamine.

Design: Comparative study.

Setting: A dermatological clinic and a research laboratory.

Participants: Eighteen patients with atopic dermatitis (AD) and 6 patients with chronic plaque-type psoriasis as well as 14 healthy control subjects.

Interventions: Histamine prick was performed in lesional and nonlesional skin of patients and in control subjects.

Main Outcome Measures: Axon reflex flare and wheal were measured planimetrically, and the itch intensity was rated on a numerical scale (0-10).

Results: In nonlesional skin of patients with AD, itch intensity and axon reflex flare were both significantly smaller compared with controls (mean ± SEM maximum itch, 1.5 ± 0.3 vs 3.1 ± 0.2 [P < .05]; mean ± SEM diameter, 12.3 ± 2.0 vs 25.3 ± 2.5 mm [P < .01]). In lesional skin of patients with AD, on the contrary, massive itch was provoked (maximum itch, 4.4 ± 0.3), although flare was relatively small (diameter, 16.1 ± 3.4 mm). Itch ratings in patients with psoriasis were low both in lesional and nonlesional skin (maximum itch, 1.3 ± 0.6 and 1.0 ± 0.4, respectively).

Conclusion: As the area of axon reflex flare is an indirect measure of activity in primary afferent neurons, our results suggest a decreased activation of peripheral pruriceptors in patients with AD. The massively increased itch in lesional skin of patients with AD might therefore be based on sensitization for itch in the spinal cord rather than in primary afferent neurons. This sensitization does not appear to be simply based on skin inflammation because histamine-induced itch was not augmented in lesional skin of psoriasis.

Arch Dermatol. 2003;139:1455-1458

THE NEUROPHYSIOLOGICAL basis for the itch sensation has been clarified by recent findings, which provided evidence for a neuronal system dedicated to itch consisting of specific primary afferent and spinothalamic projection neurons. This dedicated neuronal system can explain the mechanism of itch provoked by the pruritogen histamine. Afferent neurons activated by histamine (pruriceptors) are insensitive to mechanical stimulation and have very high electrical and thermal thresholds. These neurophysiologically assessed characteristics are not fully consistent with the clinical pattern observed in patients with chronic pruritus. For instance, in atopic dermatitis (AD), itch is also evoked by weak mechanical stimulation, such as in wool’s contact to the skin, which is at variance with the insensitivity of pruriceptors to mechanical stimulation. Moreover, histamine sensitivity of patients with AD is equal or even reduced when tested in nonlesional skin.

See also pages 1463, 1475, and 1479

It is well known that in inflammatory pain conditions, peripheral nociceptors can increase their sensitivity (peripheral sensitization) and contribute to the clinical pain. Simultaneously, the spinal processing of the noxious signals can be facilitated (central sensitization) and worsen the pain of the patient. Neurogenic plasticity leading to sensitization is also known to occur for the processing of itch following histamine stimulation. Recently, it was even shown that histamine can induce pain instead of itch in patients with chronic pain.
study, we explored lesional skin's sensitivity to histamine in AD to assess a potential sensitization of peripheral pruriceptors in the inflamed skin or a putative sensitization of the central processing of itch in these patients. To verify the results, data were compared with nonlesional skin of patients with AD, healthy controls, and also another inflammatory skin disease (chronic plaque-type psoriasis (PSO)).

**METHODS**

**SUBJECTS**

Study subjects comprised 18 patients with AD (11 women and 7 men; mean ±SD age, 24.5 ± 4.3 years), 6 patients with PSO (3 women and 3 men; mean ±SD age, 27.5 ± 3.3 years), and 15 healthy volunteers (9 women and 6 men; mean ±SD age, 28.7 ± 5.1 years). The diagnoses of AD (criteria by Hanifin and Rajka) and psoriasis vulgaris were verified by a dermatologist. All patients with AD had acute pruritic dermatitis with a typical distribution. All the patients with PSO had typical psoriasis with plaques that were diagnosed histologically as psoriasis vulgaris. Their mean ±SD Psoriasis Area and Severity Index (PASI) score was 16 ± 9.1. None of the participants used any oral or topical medication at least 1 week prior to the experiment. This study was approved by the local ethic committee, and informed consent was obtained from all the participants.

**HISTAMINE SKIN PRICK**

Ringer's solution (20 µL) containing 0.1% histamine was dropped onto the skin and pricked by the tip of a 27-gauge needle (BD Medical Systems, Drogheda, Ireland). The prick tests were performed in lesional skin areas in the patients with AD (antecubital fossa, ×17; popliteal fossa, ×1) and in visually nonlesional skin sites of the same patients in the corresponding contralateral sites. They were also performed in lesionsel (elbow) and nonlesional (contralateral sites) skin of the patients with PSO. In all healthy control subjects, histamine prick tests were performed in the antecubital fossa.

**PSYCHOPHYSICS**

The intensity of the evoked sensation was assessed by the participants on a numerical scale of 0 (no sensation) to 10 (the maximum sensation imaginable). They were asked to give separate ratings for the itch and pain sensation at 10-second intervals following the prick test.

**FLARE AND WHEAL**

The visually estimated longest and shortest axes of the evoked flare and wheal areas were measured 10 minutes after the prick test in patients with AD and healthy controls. The average of the long and short axes was regarded as the diameter of area and used for statistical analysis. Histamine-induced flare development in lesional skin could not be clearly identified in 8 patients with AD, since the flare reaction did not clearly separate from the eczema’s redness.

**STATISTICS**

The area under the curve of itch ratings, maximum itch ratings, and diameters of flare and wheal were compared between normal skin of healthy volunteers and lesional as well as visually nonlesional skin of patients with AD. Maximum itch ratings were compared also with lesional and nonlesional skin of patients with PSO. The statistical analysis was performed by a Kruskal-Wallis test. Bonferroni tests (Dunnet’s type) were applied for multiple comparisons. P values less than .05 were regarded as significant.

**RESULTS**

**ITCH RATINGS**

Histamine prick tests provoked an intense itch sensation in healthy subjects, which peaked at about 1 minute and then gradually declined. Fifteen minutes after histamine administration, itch sensation had virtually subsided (Figure 1). When prick tests were performed in nonlesional skin of patients with AD, itch ratings increased more slowly, reached their maximum between 2 and 3 minutes, and were significantly lower compared with the controls. However, itch ratings also declined gradually thereafter and did not show significant differences to the control group.

In contrast, histamine prick tests in lesional skin of patients with AD provoked a massive itch sensation that peaked about 2 to 3 minutes after the application. The ensuing gradual decline of itch ratings was particularly slow: 10 minutes after the application, when itch ratings in the control group and nonlesional AD skin already had subsided, patients with AD still reported a moderate itch in...
their lesional skin. Even after 20 minutes, a distinct pruritus was still perceived. The area under the curve (mean ± SEM) of itch ratings calculated for 20 minutes after pricking was significantly larger in AD lesional skin compared with skin from healthy volunteers (control) and AD nonlesional skin (254 ± 381 vs 850 ± 123 and 719 ± 254, respectively [P < .001 for both]). Maximum itch rating (mean ± SEM) was significantly higher in AD lesion compared with control and AD nonlesion groups (4.4 ± 0.3 vs 3.1 ± 0.2 [P < .01] and 1.5 ± 0.3 [P < .001]). Additionally, maximum itch (mean ± SEM) was significantly lower in AD nonlesional skin compared with skin from the control group (1.5 ± 0.3 vs 3.1 ± 0.2 [P < .01] and 1.5 ± 0.3 [P < .001]).

**FLARE AND WHEAL**

As might be expected from the lower itch ratings, the diameter of the axon reflex erythema (neurogenic flare) was also significantly smaller in nonlesional skin of patients with AD than in the control group (mean ± SEM diameter, 12.3 ± 2.0 vs 25.3 ± 2.5 mm [P < .01]). In contrast, the neurogenic flare in lesional skin did not differ significantly from nonlesional AD skin and was smaller compared with healthy controls, albeit this difference did not reach statistical significance. The wheal reaction did not differ significantly between lesional and nonlesional AD skin and controls (Figure 2).

**COMMENT**

In this study, we have confirmed previous reports that demonstrated nonlesional skin of patients with AD is less sensitive to histamine stimulation compared with skin of healthy volunteers. The reduced histamine sensitivity equally affects the maximum itch ratings and the extent of the neurogenic flare reaction. This flare reaction is based on an axon reflex and increases with the number of action potentials generated by the peripheral neuron. The area of the neurogenic flare is therefore an indirect measure of activity in primary afferent neurons excited by the administered histamine. Thus, in nonlesional skin, lower itch ratings and smaller flare reactions indicate a weaker response of the primary afferent neurons that underlies the alleviated itch sensation in these patients.

The most intriguing result of this study is the massively enhanced itch following histamine prick tests inside the eczema, which was not accompanied by an increased neurogenic flare reaction. Obviously, there is a mismatch of a reduced activation of peripheral histamine sensitive “itch fibers” (pruriceptors), as indicated by the smaller flare reaction, and the augmented perception of itch.

An increased sensitivity of the spinal itch processing might explain this phenomenon. Central sensitization for itch has been described previously. In these studies, a conditioning peripheral histamine stimulus changed the spinal processing such that mechanical stimuli (eg, touch and pinprick) applied adjacent to the prestimulated site were felt as itch. Yet only mechanical stimuli were found to provoke increased itch sensation, whereas in our study, chemically induced itch was enhanced. Facilitated spinal processing (“lower-itch threshold”), which even overrides a reduced peripheral pruriceptive input, could offer an explanation for the enhanced perception of itch.

There are already hypotheses of lowered itch thresholds based on human psychophysics: LaMotte et al report of delayed but increased and long-lasting histamine-induced itch when the injection site had been transiently anesthetized. The authors suggest that the injection pain would normally increase the central itch threshold. As the local anesthetic abolishes the injection pain, this threshold increase does not occur, and thereby the itch processing is facilitated. In this respect, it is interesting to note that histamine induces ongoing activity in pruriceptors, which by far outlasts the perception of itch. Thus, there is ongoing activity in pruriceptors after histamine application for about 1 hour, albeit at a low frequency. This low level of ongoing activity following histamine application is not felt as long because the spinal threshold is high enough to “ignore” this peripheral signal. It would therefore be conceivable that our patients with AD felt more intense itch because of a lower central itch threshold for input from their lesional skin.

Figure 2. Axon reflex flare induced was significantly smaller in nonlesional skin of patients with atopic dermatitis (AD) and also reduced in their corresponding lesional skin site compared with healthy controls. Wheal size was not significantly different among the 3 groups. Data are means ± SEM.

Although a lower central itch threshold is a good explanation for the present observations, our results do not prove its existence. Only electrophysiological recordings of the neuronal activity of pruriceptors could provide direct evidence. However, this information is very difficult to obtain, since pruriceptors only constitute a minor percentage of afferent fibers and, even worse, the predominant location of the AD lesions is technically not suitable for recording the supplying skin nerves.

Another approach to prove the induction of central sensitization for itch is the exploitation of ongoing activity of pruriceptors, which is apparently required to sensitize spinal pruriceptors. It is remarkable that ongoing activity in peripheral pruriceptors has already been.
Figure 3. The results of this study indicate that central neuronal sensitization (lowered central itch threshold) could lead to intense itch sensation in lesional skin of patients with atopic dermatitis (AD), although their primary afferent neurons would be only weakly activated by histamine.

verified by direct nerve recordings in a patient with chronic itch.²⁷

Central modulation of itch processing would also add a new perspective on stress-induced itch, because stress-induced descendent analgesia might directly facilitate spinal itch processing by inhibition of pain-mediating interneurons. This kind of itch facilitation would not require activation of peripheral afferents nerves via increased levels of stress hormones.

It is obvious that sensitivity of neurons inside an inflammatory lesion might be modified by the presence of a variety of inflammatory mediators. However, our results indicate that excessively increased histamine-induced itch in lesional skin is not simply based on skin inflammation, since there was no increase of histamine-induced itch in psoriatic lesions. It is yet unclear which particular mediator or which pattern of mediators is responsible for the activation of pruriceptors inside an itchy lesion, but recent results indicate that augmented signaling via protease-activated receptors (PAR-2) in the lesions might contribute to itch in AD.²⁸

There is no doubt that therapeutic measures have to focus on the reduction of local inflammation. However, for the treatment of pruritus in AD, a facilitated central processing of itch should also be considered. There are already some drugs available that are thought to exert antipruritic effects by a central mode of action. For example, antagonists of the µ-opioid receptors have been shown to diminish experimental itch²⁹ and act an-
duced by epicutaneous histamine application in atopic dermatitis and controls.

REFERENCES

2. Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to his-

Mannheim, Germany (e-mail: martin.schmelz@anaes .ma.uni-heidelberg.de).