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Mechanically evoked itch in humans

Miyuki Fukuoka, Yoshiki Miyachi, Akihiko Ikoma *

Department of Dermatology, Graduate School of Medicine, Kyoto University, Japan

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ABSTRACT

When a newly developed experimental method to vibrate vellus hairs on human skin was applied to the face and arm in healthy subjects, intense itch was reproducibly induced on the face, but not on the arm, without any flare reactions. In contrast to histamine-induced itch, mechanically evoked itch was not characterized as burning or stinging by any subjects, and was resistant to histamine H_1-receptor antagonists. When the stimulation was continued for 10 min, mechanically evoked itch reached the maximum intensity within 10 s, but gradually attenuated after 60 to 90 s and was rarely perceivable at the end of stimulation. When the stimulation was discontinued at 90 s, mechanically evoked itch rapidly attenuated after the end of stimulation, but took more than 10 min before it completely diminished. These results indicate a possible involvement of C-tactile neurons in mechanically evoked itch because they have consistent characteristics such as low mechanical thresholds, intermediate adaptation, after discharge, favorable response to slowly moving stimuli, and fatigue during repeated mechanical stimulation, although it needs to be confirmed by future microneurographic studies. Touch-alloknesis was present in the adjacent skin area until mechanically evoked itch completely diminished, supporting the hypothesis that itch sensitization can be caused by a continuous activation of peripheral itch neurons whether or not they are histamine-sensitive C nerves. In conclusion, this study provides direct evidence of mechanosensitive nerves involved in itch in human skin. The purity of mechanically evoked itch without any pain-related sensory components is a major advantage for investigating the differentiation of itch from pain.

1. Introduction

Itch had generally been recognized as a part of pain, as in the intensity hypothesis by Max von Frey [7], before the hypothesis of the labeled line for itch was suggested by the finding of mechanoinsensitive C-fibers and spinothalamic tract neurons responding to histamine [2,25]. Recent findings of the involvement of gastrin-releasing peptide and its receptor in itch-specific pathways [32] as well as distinct subsets of transient receptors potential A1 – positive neurons in chloroquine-induced itch [36] have strengthened the labeled-line hypothesis. On the other hand, the findings that polymodal C-fibers and polymodal spinothalamic tract neurons are activated in association with cowhage-induced itch [13,18] as well as that nociceptive myelinated nerves are involved in cowhage-induced itch [21] are rather contradictory to the labeled-line hypothesis. However, it is still an open question whether the cowhage-induced activation of polymodal C-fibers represents itch, or possibly only the pain-related sensory components such as pricking, stinging, and burning sensations that frequently accompany cowhage-induced itch [20]. The simplest way to solve this question would be to demonstrate mechanically evoked itch similar to cowhage-induced itch in quality and intensity. In reality, however, mechanical stimulation to the skin by von Frey filaments, which supposedly coactivates large myelinated fibers, can only evoke tactile sensation, not itch, even though it activates cowhage-sensitive neurons according to electrophysiological studies [18]. Moreover, reproducible mechanically evoked itch that is comparable to histamine- or cowhage-induced itch in intensity and quality has been shown only under specific conditions accompanied by itch sensitization, which is touch- or pinprick-evoked itch in a surrounding area of experimentally induced or disease-caused itch [10,23], but not under normal healthy conditions.

It is not only cowhage but also histamine and electrical stimulation that very frequently evoke itch and pain at the same time [11,15,30]. Although most animal studies use scratching behavior as the sign representing itch sensation to differentiate itch from pain, scratching does not always reflect itch but also pain [26]. One solution for this problem is a recently reported cheek application model in mice in which itch causes scratching but pain causes wiping [29]. However, there still remains the question of whether scratching on the cheek reflects pure itch, or possibly reflects a

* Corresponding author. Address: Department of Dermatology, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: akiikoma@kuhp.kyoto-u.ac.jp (A. Ikoma).

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mixed sensation of itch and pain. Therefore, the cheek application in mice is a useful but not perfect model to differentiate itch from pain. The zero-availability of experimental stimuli for human subjects that can constantly evoke itch without any simultaneous pain-related sensory components accompanying it is thus apparently a major obstacle in studying the differentiation of itch and pain.

The present study deals with our newly developed experimental method with mechanical stimuli to reproducibly evoke intense pure itch in healthy human subjects without any pain-related sensations, which strongly supports the presence of mechanosensitive nerves involved in itch. This method is supposed to be highly useful for future investigation on differentiation of itch and pain.

2. Materials and methods

2.1. Subjects

Ten healthy Japanese volunteers (6 men and 4 women ages 32.0 ± 6.5 years, mean ± SD), who had taken no medications for the previous 2 weeks, participated in the present study after they gave written informed consent. The study was approved by the internal ethics committee at Kyoto University.

2.2. Overview of study design

The following 6 sessions of experiments were performed by the same investigator in the same subjects with at least 1-week intervals between each session. The room temperature was kept at 23°C throughout the study.

In the first session, mechanical stimulation using the below-mentioned special probe was applied to vellus hairs of the chin, cheek, and forehead of all subjects and male beard instead of vellus hairs in the male subjects. Light touching of the chin by a cotton swab was also performed in all subjects as a control. The maximum intensity of itch during a 90-s stimulation was assessed.

In the second session, mechanical stimulation was applied to the chin 4 times with intervals that were enough for itch to diminish. The first and fourth ones were the standard stimulation with vibration of the probe and with contact to vellus hairs. In the second one, the probe vibrated without contact to vellus hairs. In the third one, the probe contacted to vellus hairs but was not vibrated.

In the third session, histamine H_1 receptor antagonist (H_1 blocker) and its placebo were orally administered in a randomized, double-blind and crossover manner with a 1-week interval between administrations of H_1 blocker and placebo. Three hours after the H_1-blocker/placebo administration, mechanical stimulation was applied for 90 s to the face and, after a 15-min interval, to the arm. After another 15-min interval, histamine iontophoresis was applied for 60 s to the face and, after a 15-min interval, to the arm. Itch sensation and flare reaction were assessed during the 90-s mechanical stimulation or for 90 s after the 60-s histamine iontophoresis. At the end of the session, the subjects were given questions to characterize in detail the itch sensation they felt.

In the fourth session, mechanical stimulation was applied to the chin for 10 min, and then, after a 15-min interval, histamine iontophoresis to the arm for 10 min. Itch intensities were continuously assessed during the 10-min stimulation/iontophoresis. In the fifth session, touch-alloknesis was assessed on the face at 3 different time points after the 90-s mechanical stimulation to the face. In the sixth session, mechanical stimulation with different frequencies (1 to 50 Hz) and amplitudes (0.2 to 1.0 mm) was applied to

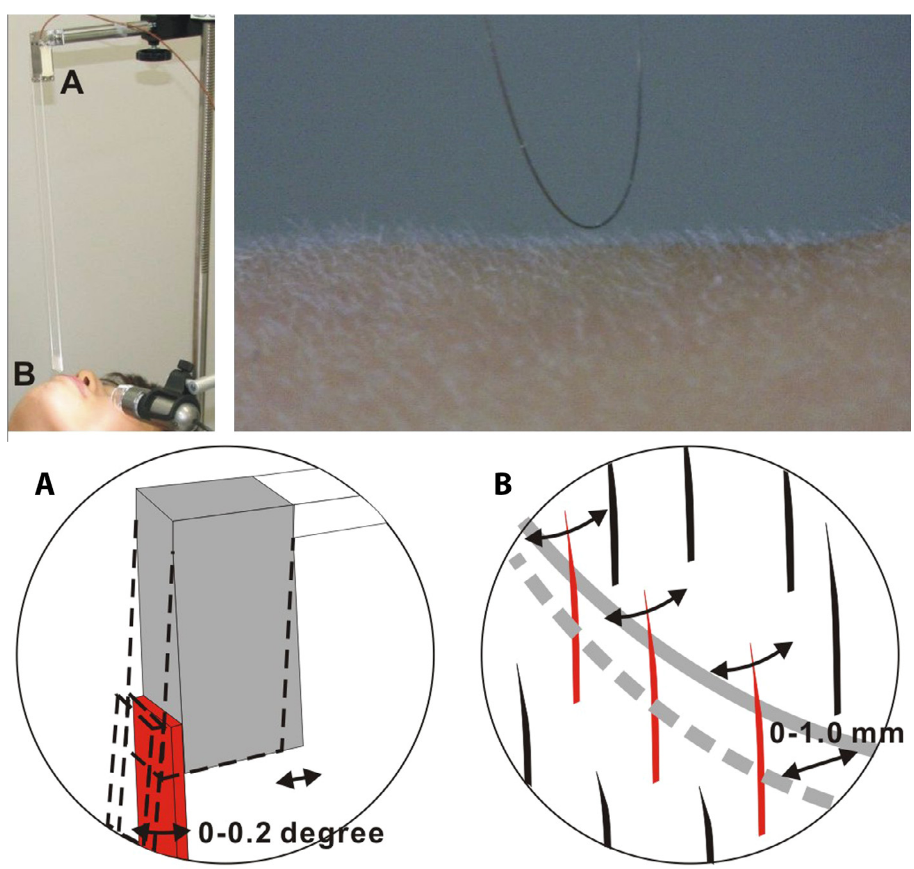

Fig. 1. The distant (upper left) and close-up (upper right, lower) views of mechanical stimulation on the face. The electrically controlled piezoelectric actuator (A) horizontally vibrated in the range of 0° to 0.2° at a frequency of 1 to 50 Hz, which led to a horizontal vibration of the stainless-steel wire loop (B) with an amplitude of 0 to 1.0 mm. The wire loop could touch and vibrate only vellus hairs, not the skin surface.