Neuroselective transcutaneous electric stimulation reveals body area–specific differences in itch perception

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Background: Electrically evoked itch has been reported, although the electrodes, the frequency, and the pulse duration used were not standardized.

Objective: To examine whether a neuroselective transcutaneous electrical stimulator (NTES; Neurometer; Neurotron, Inc, Baltimore, Md) can evoke itch and whether it can provoke itch on any body area.

Methods: Twelve healthy subjects were stimulated on 30 body sites by 5 Hz alternating current produced by the NTES. We classified the evoked perceptions into two sensations (with and without itch) and divided the examined sites into 7 groups: G1, head and neck; G2, arm; G3, palm; G4, the dorsal surface of the hand; G5, knee and leg; G6, dorsal foot; and G7, ankle. The data were then statistically analyzed.

Results: The NTES preferentially evoked itch at the G4 and G7 sites, and a sensation without itch at the G1 site.

Limitation: Tests were performed on limited body areas.

Conclusion: The NTES can provoke itch, it was discovered that there are body area–specific differences in itch sensation. (J Am Acad Dermatol 2006;55:996-1002.)

Itch has been defined as an unpleasant feeling associated with the urge to scratch. Itch can be directly evoked in the skin by chemical mediators and by physical and thermal stimuli.[1,2] A review by Staender et al[1] lists the chemical mediators that have been reported to induce itch. Among them, however, histamine-induced itch by iontophoresis is a reliable method and has been used widely to study responses to flare and local edema.[3] Recently, microneurography has demonstrated that one subset of primary afferent C-fibers is almost exclusively histamine sensitive and is probably the primary afferent whose activity elicits the itch sensation, suggesting the presence of a new class of afferent nerve fibers.[4]

As for physical stimuli, electrically evoked itch has also been reported by several authors,[5-8] although the electrode, frequency, and pulse duration used for the electric stimulation varied from study to study. In addition, the electrodes, the pulse generator, or the electric circuit was constructed by each individual laboratory. Therefore, it is not easy for other laboratories to duplicate their experiments.

Recently, it has been demonstrated that a commercially available neuroselective transcutaneous electrical stimulator (NTES; Neurometer; Neurotron, Inc, Baltimore, Md), enables us to evaluate the pain sensitivity quantitatively by using different parameters, such as the current perception threshold (defined as the minimum stimulus that evokes some kind of sensation), the pain perception threshold (the minimum stimulus that evokes pain), and the

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pain tolerance threshold (the maximum stimulus that can be tolerated). This technique has been used in various fields as a tool for the clinical evaluation and management of a variety of neurologic disorders.[9-17] In contrast to pain, however, to our knowledge, there has been no report that examined the provocation of itching by NTES.

The NTES generates three different constant alternating current sinusoid waveform stimuli at frequencies of 2000 Hz, 250 Hz, and 5 Hz that are thought to selectively activate different subpopulations of sensory nerve fibers: the large myelinated fibers (Aβ-fibers), the small myelinated fibers (Aδ-fibers), and the unmyelinated fibers (C-fibers), respectively.[18] Recently, Koga et al[19] demonstrated, by examining the action potentials of rat dorsal root ganglion, that transcutaneous sine wave stimuli at 5 Hz stimulates mainly C-fibers. Therefore, it would seem possible to evoke itch by stimuli at 5 Hz. The purpose of this study was to examine whether the NTES can evoke itch and, if so, to clarify whether the electric stimulation can provoke itch at any area on the body.

METHODS

Subjects and electrical stimulation

Twelve healthy subjects (7 males and 5 females aged 23.6 ± 2.5 years) participated in the study. With the patient in a sitting position, the evaluation was performed on 30 sites, including the head, neck, forearms, the dorsal surface of the hands, the palms, legs, and feet (Fig 1). The current was delivered to the skin by a pair of 1-cm diameter gold surface electrodes that were covered by a thin layer of electroconductive gel and separated by 1.7 cm with a clear mylar spreader (Neurotron, Inc). The NTES delivered a 5 Hz alternating sinusoid waveform current and its intensity was increased until the subjects perceived some kind of sensation, such as pain, itch, or painful itch. The current perception threshold was defined as the minimum current intensity that the subjects consistently perceived as a sensation (itch, pain, painful itch, etc). The pain sensation included the sensations of pricking, stinging, and piercing. After continuous stimulation for 1 minute at the current perception threshold, the current intensity was increased to 1.5 times the current perception threshold, and then maintained for another minute. During this process, the subjects were asked whether they became aware of any qualitative change in the sensation. When the subjects did not perceive any sensation by the maximum current intensity (1.50 mA), the data was not obtained. In six volunteers, we added the electrical stimulation on three representative test sites (sites 7, 15, and 26) twice at an interval of 1 week. We also assessed alloknesis, which was defined as the enhanced sense of itch evoked by innocuous stroking, on the wrist skin of five subjects during the itch-inducible stimulation. This study was approved by the ethics committee of Tohoku University Graduate School of Medicine, and all subjects gave informed consent before the examinations.

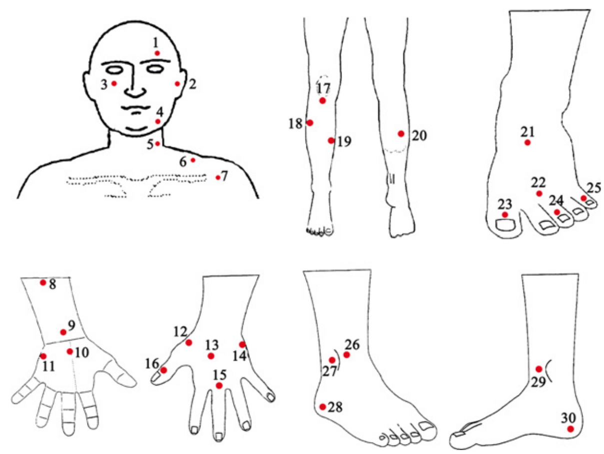

Fig 1. Distribution of the examined sites. Evaluations were performed on 30 sites of the head, neck, arms, the dorsal surface of the hands, and the palms, legs, and feet.

Statistics

We compared the current perception threshold of itch with that of pain on each examined region by Wilcoxon rank sum test.

To analyze body area−specific differences in the induction of itch, we classified the perceived sensations into two categories: those with itch and those without itch. We analyzed the differences in sensation among the examined regions statistically. All of the test sites were divided into 7 groups (G1, head and neck; G2, arm; G3, palm; G4, the dorsal surface of the hand; G5, knee and leg; G6, the dorsal surface of the foot; and G7, ankle), and the evoked perceptions were divided into two groups (sensation with itch and without itch). The χ^2 test was applied to each group. Next we examined the effects of the examined regions on the difference in evoked perceptions by 2-way ANOVA. When the analysis showed a significant difference, we identified the groups whose differences accounted for the significant P value by 2-way ANOVA.

Results

We performed 360 examinations (30 sites each for 12 subjects). At the current perception threshold, itch, pain, and painful itch were the main sensations that the subjects felt in these experiments (307 examinations; 85.3%). The others were cold, warm,

Table I. NTES current intensity required to evoke the perceptions*

Test site		Dermatome	Itch mA†	Pain mA†
Head and neck	1	Ophthalmicus nerve	0.07 ± 0.03	0.22 ± 0.04
	2	Mandibularis nerve	0.43 ± 0.03	0.17 ± 0.05
	3	Maximallaris nerve	0.18 ± 0.04	0.27 ± 0.06
	4	Mandibularis nerve	0.24 ± 0.03	0.21 ± 0.04
	5	C3	0.14 ± 0.02	0.11 ± 0.03
	6	C4	0.2 ± 0.01	0.07 ± 0.02
Arm	7	C5	0.03	0.22 ± 0.04
	8	C6/7/8	0.07 ± 0.02	0.11 ± 0.03
	9	C6/7/8	0.15 ± 0.03	0.15 ± 0.03
Hand	10	C6/7/8	0.43 ± 0.05	0.55 ± 0.05
	11	C8	0.45 ± 0.03	0.63 ± 0.04
	12	C6	0.15 ± 0.03	0.19 ± 0.04
	13	C7	0.10 ± 0.02	0.16 ± 0.03
	14	C8	0.13 ± 0.03	0.17 ± 0.03
	15	C7	0.11 ± 0.03	0.19 ± 0.05
	16	C6	0.54 ± 0.05	0.62 ± 0.05
Knee	17	L4	0.16 ± 0.04	0.31 ± 0.05
Leg	18	L5	0.15 ± 0.03	0.25 ± 0.05
	19	L4	0.32 ± 0.03	0.28 ± 0.05
	20	S1	0.31 ± 0.02	0.19 ± 0.04
Foot	21	L4/L5	0.19 ± 0.04	0.29 ± 0.06
	22	L5	0.29 ± 0.05	0.47 ± 0.05
	23	L4/L5	0.66 ± 0.04	1.25 ± 0.06
	24	L5	0.24 ± 0.04	0.32 ± 0.03
	25	S1	0.74 ± 0.08	0.69 ± 0.06
	26	L5	0.29 ± 0.05	0.39 ± 0.06
	27	S1	0.22 ± 0.04	0.20 ± 0.04
	28	S1	0.58 ± 0.06	0.46 ± 0.04
	29	L4/S	0.30 ± 0.05	0.23 ± 0.04
	30	S2	0.45 ± 0.06	0.50 ± 0.06

*We delivered a 5-Hz alternating sinusoid waveform current by the NTES and increased the current intensity until the subjects perceived some kind of sensation, such as pain, itch, or painful itch. When the subjects felt painful itch, the data of the current intensity were included in both the pain and itch groups. The examined sites were named by the dermatome which involves them.
†The amounts of the current are shown as mean ± SEM.

and touch, although the number of subjects who felt those sensations was very small (22 examinations; 6.11%). Table I presents the mean ± SEM of the current intensity that provoked itch or pain. In the case of the subjects who perceived painful itch, the data were included in both the itch and pain groups. We could not find a statistically significant difference between the current intensity required to induce itch and that which induced pain on any examined sites (Wilcoxon rank sum test).

While the current intensity was maintained at the current perception threshold, or while it was increased up to 1.5 times the current perception threshold and then maintained for 1 minute, several subjects recognized some qualitative changes in sensation, such as from pain to itch or from itch to pain. Table II shows the results. A change from pain to itch occurred in 45 examinations. Fifty percent of the subjects perceived a change from pain to itch, especially on the dorsal surface of the hand (site 15) and inner ankle (site 29). Alternatively, a change from itch to pain occurred in only 15 examinations. The change from pain to itch arose in 21 examinations (46.7%) while maintaining the current perception threshold and in 24 examinations (53.3%) while increasing the intensity. A change from itch to pain was only reported when increasing the current intensity.

Figure 2 summarizes the perceptions the subjects experienced during the entire process of this experiment, including the qualitative changes. Our results reveal that the type of sensations evoked by the electric stimulation are highly body area−specific. Namely, the subjects felt pure pain at 51/72 (70.8%) examinations of the head and neck (sites 1-6), and at 22/36 (61.1%) examinations of the legs (sites 18-20).

Table II. Qualitative changes of perceptions during the electrical stimulation*

	Pain → itch	Itch → pain
Number of examinations (360 total)	45	15
Change during maintaining the CPT	21	0
Change during increasing intensity	24	15
Test sites	Wrist, dorsal surface of the hand, ankle	No tendency

*We delivered a 5-Hz alternating sinusoid waveform current and increased the current intensity until the subjects perceived some kind of sensation, such as pain, itch, or painful itch. The current intensity was maintained for 1 minute, then increased up to 1.5 times and maintained for 1 additional minute. During this process, they were asked whether they became aware of any qualitative change in the sensation.

In contrast, the subjects perceived itch or some sensations mixed with itch at 34/48 (70.8%) examinations of the dorsal surface of the hand (sites 12-15), and at 37/48 (77.1%) examinations of the ankles (sites 26-29). To confirm the reproducibility of the results, six subjects received another series of electrical stimulations 1 week after the first experiment. Among 18 examinations performed on the three representative sites (sites 7, 15, and 26 for all 6 subjects), 83.3% perceived the same sensation. Furthermore, when we examined whether the stimulation by the NTES evoked alloknesis, 5 of 5 subjects claimed to experience alloknesis during the electrical stimulation.

To determine the effects of the examined regions on the kinds of evoked sensations, statistical analysis was performed. All of the test sites were divided into 7 groups (G1-G7) and the evoked perceptions were divided into 2 groups (sensation with itch and without itch) as shown in Table III. At first, we confirmed that there was no statistical difference in the ratio of the subjects who perceived itch sensation at the examined sites within each group by χ^2 test. Then we conducted 2-way ANOVA for comparison among groups. The results indicated that there was a significant difference in the ratio of the subjects who experienced itch sensation ($.01 < P < .05$) and that the test site had a significant effect on the kind of sensation experienced ($P < .01$). Next, to identify the groups whose differences accounted for the significant P value, 2-way ANOVA was applied to pairs of groups (Table IV). A significant interaction implies that there was a significant effect of the region on the kinds of evoked sensations. Table IV, showing the results of the analysis between the pair of groups, indicated that G4 (the dorsal surface of the hand) and G7 (ankle) were more specific for the itch sensation, whereas G1 (head and neck) was more specific for the sensation without itch.

DISCUSSION

In this study, we clearly demonstrated that the NTES could provoke an itch sensation and that the same electric stimulation could provoke different sensations depending on area of the body that was stimulated. Electrically evoked itch has been previously reported.[5-7] Ikoma et al[20] succeeded in provoking intense itch by transcutaneous electrical stimulation using very localized electrodes. The induced itch was characterized by delayed perception and long pulse duration (>2 ms), which suggested that unmyelinated afferents underlie the electrically evoked itch. However, this electrically evoked itch was unique in the lack of an axon reflex flare, lower electrical threshold, and high frequency (>50 Hz) required for its induction. Although the electrical stimulation we used was different in terms of the electrodes, the waveform, the pulse duration, and the frequency compared to that employed by Ikoma et al,[20] the itch induced in our study shared several characteristics with that provoked by their device. Both could provoke itch with low current intensity and the induced itch was accompanied by alloknesis, but not by an axon reflex flare. In general, it is well known that the stimulation of C-fibers is accompanied by an axon reflex flare.[21,22] However, the electrically evoked itch induced by Ikoma et al and the itch we induced was not accompanied by the axon flare reflex. Recently, Schmelz et al[23,24] reported that there were two major groups of C-fibers in human skin—mechano-responsive and mechano-inresponsive—and that mechano-responsive C-fibers did not mediate the axon reflex flare. Therefore, the electrical stimulation may stimulate mechano-responsive C-fibers, although more precise studies will be required to determine which subgroup of C-fibers is responsible for the electrically evoked itch.

However, there were remarkable differences between the sensations induced by these two procedures. Although the NTES provoked itch, the subjects felt different kinds of itch sensation, like pure itch and itch plus pain. Moreover, some subjects felt a change in the sensation from pain to itch or from itch to pain. In contrast, the sensation provoked by Ikoma et al[20] was pure itch at a stimulus frequency of 50 Hz and pulse duration of 2 ms in significant percentages of the trials. Because

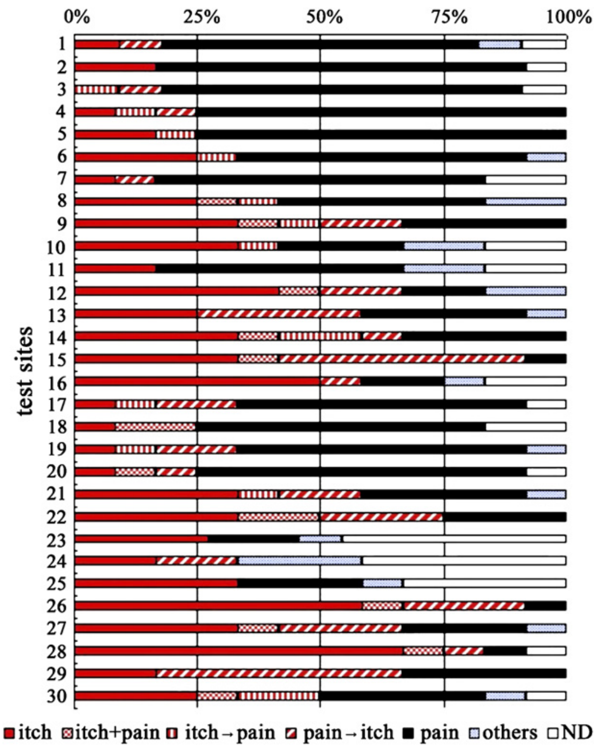

Fig 2. Summary of the sensations induced by the NTES. Twelve healthy subjects were evaluated on 30 sites of the head, neck, arms, the dorsal surface of the hands, and the palms, legs, and feet for the sensation induced by NTES. The current intensity was increased until the subjects perceived some kind of sensation described as pain, itch, or painful itch. We defined this current intensity as "current perception threshold." After continuous stimulation for 1 minute at the current perception threshold, the current intensity was increased up to 1.5 times the current perception threshold, and then maintained for another minute. During this process, the subjects were asked whether they became aware of any qualitative change in the sensation. The data are presented as the perception the subjects felt during the entire process of this experiment, including the qualitative changes. When the subjects felt a constant sensation during the process, the data were expressed as follows: *red column*, pure itch; *striped column*, painful itch; *black column*, pure pain; *blue column*, other perceptions, such as warm, cold, and touch; *blank column*, no sensation detected. When they felt the sensation change, the data were expressed as follows: *vertical striped column*, from itch to pain; and *oblique striped column*, from pain to itch. The sum of the red, cross striped, vertical striped, and oblique striped columns represents the total percentage of the subjects who felt some sensation accompanied by itch.

Table III. Ratio of the subjects who perceived itch sensation during the electrical stimulation*

Test site		No. of subjects: With itch	No. of subjects: Without itch	χ^2 test: Group	χ^2 test: Results
Head and neck	1	2	10		
	2	2	10		
	3	2	10		
	4	3	9	G1	NS
	5	3	9		
	6	4	8		
Arm	7	2	10		
	8	5	7	G2	NS
	9	8	4		
Hand	10	5	7	G3	NS
	11	2	10		
	12	8	4		
	13	7	5		
	14	8	4	G4	NS
	15	11	1		
	16	7	5		
Knee and leg	17	4	8		
	18	3	9	G5	NS
	19	4	8		
	20	3	9		
Foot	21	7	5		
	22	9	3		
	23	3	9	G6	NS
	24	4	8		
	25	4	8		
	26	11	1		
	27	8	4		
	28	10	2	G7	NS
	29	8	4		
	30	6	6		

*Evoked perceptions were classified into 2 sensations, the sensation with itch and that without itch, and divided into 7 groups composed of anatomically contiguous sites (G1, head and neck; G2, arm; G3, palm; G4, the dorsal surface of the hand; G5, knee and leg; G6, the dorsal surface of the foot; and G7, around the ankle). We examined the lack of statistical significance in the ratio of the number of subjects that perceived itch versus that of those that did not perceive itch among the examined sites within each group by χ^2 test.

Shelley and Arthur[5] demonstrated that electric stimulation provoked itch through so-called itch points, this difference may have been caused by differences in the electrodes used for stimulation. An electrode of stainless steel wire 0.1 mm in diameter can specifically stimulate itch points, while 1-cm diameter electrodes may stimulate simultaneously both itch points and points that trigger sensations other than itch.

Over the course of the examination, several subjects described some qualitative changes in the sensation, such as from pain to itch or from itch to pain. Interestingly, a change from pain to itch arose in 45 examinations, while a change from itch to pain arose in only 15 examinations. Moreover, almost all of the subjects who felt a change from pain to itch described that they could distinguish pain that would change to

Table IV. Statistical analysis of the effects of the groups of examined sites on the kinds of perceptions

		Interactions between examined regions and evoked perceptions (*P*)*
G1	G2	< .05
	G3	NS
	G4	< .01
	G5	< .05
	G6	< .01
	G7	< .01
G2	G3	NS
	G4	< .05
	G5	NS
	G6	NS
	G7	< .05
G3	G4	< .01
	G5	NS
	G6	NS
	G7	< .01
G4	G5	< .01
	G6	< .01
	G7	NS
G5	G6	NS
	G7	< .01
G6	G7	< .01

*The difference in the kinds of evoked perceptions among the examined regions was analyzed twice by 2-way ANOVA.

itch from pain that would not change. In our study, we increased the current intensity to trigger some sensation. Therefore, we could not determine whether the itch provoked by our stimulation was perceived with a delay as demonstrated by Ikoma et al.[20] However, the fact that a significant number of the subjects felt the change of sensation from pain to itch may suggest the possibility that the itch induced by the NTES is also perceived with a delay.

Interestingly, the change of sensation from itch to pain arose only when increasing the current intensity, while a change from pain to itch was reported while maintaining the current intensity in approximately one half of the cases. The inhibition of itch by painful stimuli has been shown experimentally by use of noxious thermal, mechanical, and chemical stimuli.[25] Recently, electrical stimulation via an array of pointed electrodes, a method known as cutaneous field stimulation, has also been successfully used to inhibit histamine-induced itch.[26] The change of sensation from itch to pain may be induced via the inhibition of itch by noxious electrical stimulation.

Our current study revealed statistically that the same electric stimulation could provoke a remarkable difference in the itch perception depending on the body area that was provoked. Approximately 65% of the subjects felt pure pain on the head and neck and legs, while approximately 75% of the subjects perceived itch or a mixture of itch plus pain on the dorsal hands and ankles. More than 90% of the subjects perceived some kind of itch, especially at the third metacarpophalangeal joint of the dorsal surface of the hand (site 15) and the outer ankle (site 26). Shelly and Arthur[5] had already demonstrated differences in the itch perception among various areas of the body using stimulation by the insertion of a single cowhage spicule. In their studies, although the results were not analyzed statistically, the wrist and the foot were sensitive to itch stimulation, which was consistent with our observations. Recently, Rukwied et al[27] have also demonstrated a difference in histamine-induced experimental itch between the scalp skin and forearm skin. Interestingly, the present study also demonstrated that forearms (G2) were more itch-sensitive than the head and neck (G1; Table IV). These results suggest a possible relation between the itch induced by histamine and that evoked by the NTES. Because the intradermal microdialysis conducted by Rukwied et al is somewhat invasive, it would not be easy to apply to patients with various skin disorders. The evaluation of itch sensation using the NTES can be a good alternative method to evaluate itch in various skin disorders.

To our knowledge, after the report by Shelley and Arthur,[5] in which they evaluated the density of itch points by the numbers of spicules that caused itch, itch points have not been extensively studied. There has been no report about the density of itch points in patients with atopic dermatitis (AD). Although Kobayashi et al[28] demonstrated that AD patients showed lower current perception threshold than healthy subjects, they did not clarify further the kinds of evoked sensation. Ikoma et al[20] examined the responses to electric stimulation and the histamine iontophoresis in AD patients but failed to detect any significant difference from healthy subjects. However, in their study, they examined the uninvolved skin and did not examine the density of the points that were susceptible to itch. Because several papers[29-32] have recently demonstrated that the lesional skin of AD showed increased density of intraepidermal nerve fibers, it is conceivable that this is accompanied by an increased density of itch points. Examination of the itch sensation induced by the NTES would be suitable to clarify this issue. Although there are several means to evaluate the atopic dry skin, such as by transepidermal water loss and skin conductance, whether these parameters reflect the kinds of sensation that arise is not known. Further investigations concerning the density of itch points determined by the kinds of electrically evoked sensation could be a new marker for predicting the sensitivity for itch stimulation.

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