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Perception of Histamine-induced Itch Elicited in Three Different Skin Regions

C.-F. WAHLGREN[1] and A. EKBLOM[2]

[1]Department of Dermatology, Karolinska sjukhuset, and [2]Department of Physiology II, Karolinska institutet, Stockholm, Sweden

In order to investigate whether any regional difference in itch perception exists in experimentally induced pruritus, various concentrations of histamine (1, 3.3, 10, 33 and 100 μg/ml) were injected intradermally in three different skin regions in 15 healthy subjects. The regions were 1) the volar aspect of the forearm, 2) the lateral aspect of the upper arm and 3) the upper back at scapular level. Itch perception (itch latency, itch duration, maximal itch intensity, 'total itch index') and flare reactions were studied.

A significant dose-response relationship was shown in each of the three regions for all itch variables, except itch latency, and for the flare reactions. However, no significant regional difference in itch perception was observed. The flare reaction showed a regional variation, with significantly smaller flares on the forearm than in the other two regions. ***Key words: Pruritus; Flare.***

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C.-F. Wahlgren, Department of Dermatology, Karolinska sjukhuset, S-104 01 Stockholm, Sweden.

Pruritus is a disturbing sensation irrespective of where on the body it occurs. Few studies have focused on whether experimentally induced itch is perceived equally, when elicited in different skin regions. Cormia & Kuykendall (1) compared itch thresholds to intradermally injected histamine in three body regions and found considerable variations. They stated that, in general, thresholds were lower on the leg, intermediate on the forearm, and somewhat higher on the back. When, however, Shelley & Arthur inserted single cowhage spicules into the skin of various body areas, they found the differences between subjects too large to permit any definite conclusions on differences in regional itch sensitivity (2). No systematic quantitative study of itch perception in various skin regions has followed these initial observations. A regional difference in the size of wheals (3, 4) and flares (4) produced by intradermal histamine administration is well-known. In controlled studies of pain, a sensory modality with several similarities to itch, regional differences in pain sensitivity have been reported by some authors (5), although not by others (6, 7).

To further elucidate the mechanism of itch perception, we induced itch and flare experimentally by intradermal injections of various histamine concentrations in three different body regions. Both distal and proximal skin areas were investigated in order to compare our results with those obtained in other studies of somatosensory perception.

MATERIAL AND METHODS

Subjects

Fifteen healthy volunteers, all females aged 18–37 years (median age 27), participated in the study. The subjects had no history of skin disease or present medication. They had not been sunbathing or exposed to artificial UV radiation during the previous 3 months. The study was approved by the Ethics Committee at Karolinska sjukhuset.

Experimental protocol

Three different skin regions were investigated: 1) the middle third of the volar aspect of the forearm, 2) the middle third of the lateral aspect of the upper arm and, 3) 5–15 cm laterally to the spinal column at midscapular level on the back. Each region was tested separately on one day. The order in which the different skin areas were tested was determined using a 'latin square' sequence. The intradermal injections were given by the same investigator using a double-blind technique. The injection order was randomly established on the first test day and then kept for the following two tests, which were performed within 14 days and at the same time of day. Six injections were given on each test day, 3 on the left side of the body (numbers 1, 3 and 5) and 3 on the right side (numbers 2, 4 and 6).

Injected substances

Histamine hydrochloride (ACO Läkemedel AB, Sweden) was injected intradermally in volumes of 0.01 ml in five different concentrations (1, 3.3, 10, 33 and 100 μg/ml), made by dilution with sterile pyrogen-free physiological saline containing 10% (v/v) Sörensen phosphate buffer ($Na_2HPO_4+KH_2PO_4$, 67mM), pH 7.40. Buffered saline also served as control.

Recording of itch

The intensity and duration of the provoked itch were monitored continuously for up to 15 min after each injection, using a linear potentiometer, equipped with a 100-mm visual analogue scale (VAS). The potentiometer lever, sliding along the VAS, controlled the position of a pen on a plotter out of sight of the subject. The left and right endpoints of the VAS were marked 'no itch' (0 mm) and 'maximal itch' (100 mm), respectively. The time interval between histamine injection and start/stop of itch was recorded as well as the perceived itch intensity. This allowed the calculation of itch latency (IL, sec), itch duration (ID, sec), peak value of itch (Imax, 0–100 mm) and a 'total itch index' (Tii=area under the curve, mm^2), reflecting both intensity and duration.

Recording of flare

The skin flare reaction was outlined with a marking pen on the skin 5 min after the injection and traced onto transparent plastic film from which the area (mm^2) was calculated using a planimeter (model 317, Gebrüder Haff GmbH, Pfronten, W. Germany).

Statistical methods

The dose-response relationship between the histamine concentrations and the different variables (IL, ID, Imax, Tii, flare) in each skin region was determined using a one-way analysis of variance with repeated measures (ANOVA). To test for dose discriminability in each region, comparisons between means of the separate variables for different histamine concentrations were analysed with the Tukey test. The results of saline injections were excluded from the statistical analysis.

RESULTS

Saline

Saline induced itch on one or more occasions in 7/15 subjects. The mean values (± SD) in the seven responders were as follows; IL = 18 ± 8 sec, ID = 56 ± 25 sec, Imax = 13 ± 7 mm, and Tii = 456 ± 306 mm^2. No regional difference was observed for the itch variables. Saline-provoked flare reactions tended to be more frequent and larger on the back and occurred in 7/15 subjects, with a mean area of 283 ± 54 mm^2. On the forearm and the upper arm, flares were seen in 3/15 subjects, with mean values of 167 ± 84, and 177 ± 202 mm^2, respectively.

Histamine-induced itch perception

Histamine induced no significant dose-response relationship for IL in any of the 3 different body regions investigated (Fig. 1a), but for ID, Imax and Tii this was shown in all areas (Figs. 1b-d, respectively) (F-values (4,56) between 7.385 and 14.094, $p<0.001$). The ID for 1 μg/ml histamine differed significantly from those of 10 and 33 μg/ml ($p<0.05$), and 100 μg/ml ($p<0.01$), whereas the concentrations of 3.3, 10 and 33 μg/ml did not differ significantly from one another. The Imax for 1 μg/ml differed significantly from the other concentrations ($p<0.01$), as did 3.3 μg/ml from 100 μg/ml ($p<0.05$). The differences between 3.3, 10 and 33 μg/ml were not significant. The Tii following 1 μg/ml differed significantly from those of 10, 33 and 100 μg/ml ($p<0.01$); 3.3 differed significantly from 100 μg/ml ($p<0.01$), but there was no significant difference between the 3.3, 10 and 33 μg/ml. The dose-response curves did not differ significantly between the 3 different regions.

Histamine-induced flare

The flare reactions (Fig. 1e) showed significant dose-response relationships in all regions (F-value (4,56) 93.539, $p<0.001$). Histamine 1 μg/ml differed significantly from the other concentrations ($p<0.01$); 3.3 and 10 μg/ml did not differ from one another, but both differed significantly from 33 and 100 μg/ml ($p<0.01$). The difference between 33 and 100 μg/ml was also significant ($p<0.01$). The dose-response relationships of the regions differed significantly (F-value (2,28) 6.651, $p<0.01$), with significantly less flare on the forearm than on the upper arm ($p<0.01$), or the back ($p<0.05$).

DISCUSSION

The pathophysiologic mechanisms of itch are not fully known. Psychophysical experiments must be performed on humans, as no animal models for the study of itch are established. Previous experiments on regional differences in itch have focused mainly on itch thresholds (1, 2), but recent studies indicate the usefulness of intensity ratings of itch in the study of experimentally induced pruritus (8, 9, 10). The present results accord with previous data showing that the technique with intradermal histamine injections and assessment of itch intensity, using either magnitude estimation (8) or VAS ratings (9) produces significant dose-response relationships. The relatively large variation in itch latency for the different subjects in the present study prevented any finding of a significant inverted relationship between itch latency and histamine concentration, although the data obtained were in the same range as found earlier (9). In the present study, we used 5 histamine concentrations, but not all of these could be signif-

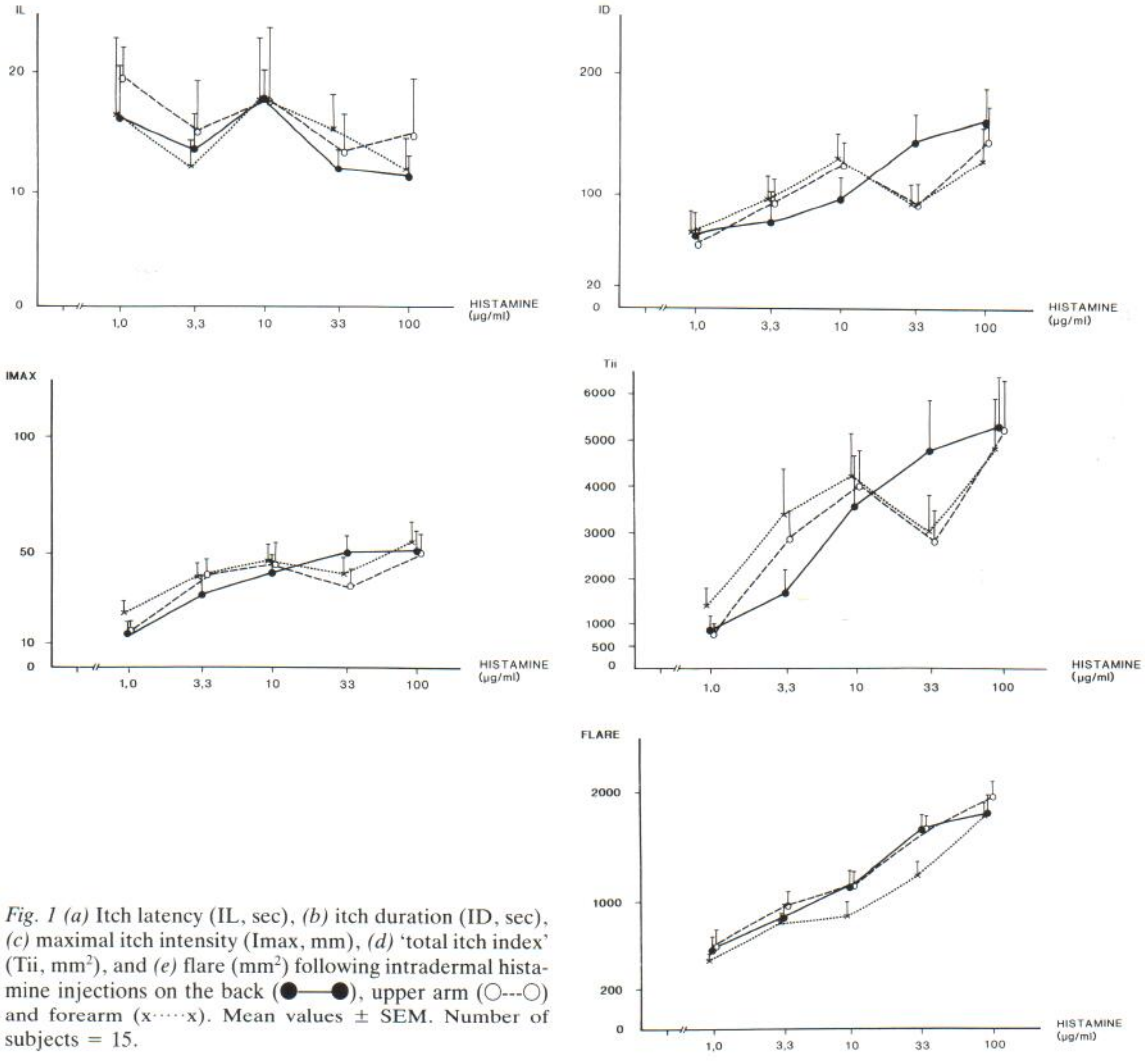

Fig. 1 (a) Itch latency (IL, sec), *(b)* itch duration (ID, sec), *(c)* maximal itch intensity (Imax, mm), *(d)* 'total itch index' (Tii, mm^2), and *(e)* flare (mm^2) following intradermal histamine injections on the back (●—●), upper arm (○---○) and forearm (x·····x). Mean values ± SEM. Number of subjects = 15.

icantly discriminated from one another by the subjects. However, the discriminability was of the same order as reported by others (8). In histamine-induced experimental itch, it might thus be possible to use a limited number of concentrations with a minimum number of injections administered to the subjects to obtain a significant dose-response relationship.

The finding that there was no significant difference in itch perception between the three skin regions was somewhat unexpected. Cormia & Kuykendall (1) stated that the histamine-induced itch threshold, in general, was lower on the forearm than on the back. Compared with proximal parts of the body, the distal parts have greater sensitivity to mechanical stimulation (11), in terms of sensory thresholds and two-point discrimination, activating myelinated A-β afferent nerve fibres. Studies of thermally-induced pain, preferentially activating C-fibres, have not indicated such a good distal-to-proximal 'gradient' as found in mechanoreception (5, 6, 7). The sensation of itch is considered to be the consequence of activity in thin afferent non-myelinated slowly conducting polymodal C-fibres (2, 12). One hypothesis is that skin perception of pain and itch may be of equal importance irrespective of where on the body it occurs, thereby explaining the lack of significant regional variation.

In contrast to the subjectively rated itch, the flare response differed significantly between the three skin regions. Such a discrepancy between itch and flare responses has been observed earlier (13). In

agreement with previous studies (3), the objective histamine-induced skin reaction was smaller on the forearm than on the back. The flare response following histamine injection is considered to be a consequence of activation of afferent sensory nerves (with a putative peptidergic release from nerve terminals) (14), mast cells and small blood vessels. These factors may all contribute to the regional differences of the flare reactions. In studies of the rat, however, an increased amount of substance-P-containing nerve fibres was found around distal joints, when compared with proximal joints of the extremities (15). Also in human skin, the amount of substance P and calcitonin gene-related peptide has been reported to be higher in the fingers than in the axilla (16). Opinions differ on the distribution of mast cells in human skin. Binazzi & Rampichini reported considerable regional variations in the number of human skin mast cells (17), whereas others could not confirm this (18).

In conclusion, intradermally injected histamine induced no significant regional variation in itch perception, but in flare reaction, with significantly smaller flares on the forearm, compared with the upper arm or the back. The mechanism for the discrepancy between histamine-induced itch perception and flare is unclear, as is the previously known regional difference in flare reaction.

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