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INVESTIGATIVE REPORT

Electrical Ear Acupuncture Reduces Histamine-induced Itch (Alloknesis)

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In order to assess an objective measure for the outcome of ear acupuncture, we evaluated the effect of electrical ear acupuncture on areas of histamine-induced alloknesis in 32 healthy volunteers. In a first assessment 5 min after histamine application on both volar forearms, 16 subjects received right ear and 16 left ear acupuncture. Immediately before and 5 min after acupuncture, alloknesis areas on both forearms were planimetrically evaluated. A second assessment was carried out 4 weeks later with the same patients. They underwent histamine application once more, but received no acupuncture. Alloknesis areas were then compared with reference to time, assessment and therapy side. Forearms relating to ipsilateral acupuncture showed significantly reduced or even no alloknesis areas after therapy. On the contralateral sides and during the "non-acupuncture" assessment 4 weeks later, alloknesis areas were significantly enlarged compared with sides ipsilateral to right and left ear acupuncture. Hence, results verify the effects of electrical ear acupuncture by objective measures. ***Key words: Electrical ear acupuncture; alloknesis; histamine provocation; itch.***

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Itch, an unpleasant sensory experience causing the desire to scratch, occurs in various dermatological diseases.

Alloknesis or "itchy skin" is a sensory phenomenon that appears in the area surrounding histamine-pretreated skin. Slight mechanical stimulation of such a skin region (e.g. stroking with a soft brush) elicits itch instead of provoking a mechanical sensation. This phenomenon has been explained by the excitation of itch-mediating central neurones by interneurones getting input from fast-conducting myelinated fibres (mechanoreceptor units). This input has to be gated by the slow-conducting polymodal unmyelinated C-fibres activated by the local pruritogenic stimulus. Alloknesis is influenced by the excitability of peripheral afferent nerve fibres, but there is strong evidence that it is mainly due to central nervous processing (1–4).

The therapeutic arsenal against pruritus is limited (5, 6). Antihistamines are the most common drugs in itch therapy. Among them olopatidine and cetirizine seem most to suppress histamine-induced pruritus as well as flare and wheal responses (7–9). Additionally there have been several promising attempts to treat itch with acupuncture. Trials have been undertaken to obtain the inhibiting effect of acupuncture and electro-acupuncture on histamine-induced itch (10, 11). Equivocal findings on the effectiveness of acupuncture may be attributable to flaws in study methodology (12, 13). Standardization of acupuncture studies is particularly difficult, due to factors characteristic for alternative methods. To start with, acupuncture is often applied in cases when there are several possible medical reasons for patients' symptoms, such as pain, which renders pathogenesis more difficult and complex (14). As a consequence, the investigator has to rely much more upon subjective statements of patients than is the case with more standardized symptoms and treatments. Therefore, in order to solve the controversy regarding the effectiveness of acupuncture, studies on acupuncture have to minimize the effects of investigator bias and lack of standardized treatment and maximize the blinding of the investigator, patient and therapist. Acupuncture research aims to investigate homogenous patient populations with specific conditions to reduce the so-called "background noise" mentioned above (15). The model of iontophoretic histamine application makes it possible to create an equal standard of pathogenesis and acupuncture point selection among all patients (10, 11). In contrast to itch reactions, alloknesis areas can be evaluated planimetrically, which makes it possible to exclude the patients' subjective experiences in response to treatment while the area of alloknesis is determined. (During the determination of the area of alloknesis it is ensured that the volunteer has no visual control).

Ear acupuncture is a technique developed in France by Paul Nogier in the 1950s (16, 17). The effects of ear acupuncture are faster and initially more intensive than serial acupuncture. Therefore it is used mainly for pain

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therapy or acute reactions such as the histamine-induced dermal disturbance applied in our model (17).

The aim of our study was to evaluate the efficacy of electrical ear acupuncture in controlling itch using the model of histamine-evoked alloknesis. Therapeutic effects are shown by changes in the alloknesis areas. Moreover, the study demonstrates that, to be effective, treatment must be applied ipsilaterally to the area of alloknesis.

MATERIAL AND METHODS

A request for volunteers was posted on bulletin boards around the university. This yielded 32 healthy volunteers who reported no atopic symptoms and were not taking any drug therapy (23 men, 9 women, age range 20–35 years; mean±SD 25±3.2 years). To the best of our knowledge there are no gender-related effects referring to alloknesis or ear acupuncture treatment, so we accepted the different number of male and female volunteers. Informed consent was obtained from all subjects and the protocol of the study was approved by the local ethics committee. Experiments were performed between 15.00h and 17.00h in a room with a temperature of 19–22˚C. The subjects stayed in the room for 15 min before histamine was applied on both volar forearm sides iontophoretically. Histamine dihydrochloride (1%) was dissolved in a gel of 2.5% methylcellulose in double distilled water. The gel was placed in the cavity of an acrylic applicator (diameter 5 mm, volume 50 µl) containing a silver-silver chloride electrode for current delivery. A larger electrode (3×3 cm) in a sponge soaked with Tyrode's solution held by the subject, was used as reference. Intensities of iontophoretic stimuli, expressed in terms of the number of histamine molecules carried into skin, follow Coulomb's law as the product of current and time (18–20). Our standardized charge was 20 mC per forearm with a current of 1 mA for 20 s.

The area of alloknesis was identified by gently stroking the surrounding skin with an interdental brush. Starting at a distance of 8 cm from the site of histamine application, the brush was passed gently over the skin in centripetal direction. In this way, the border of the itchy skin region was determined from five directions. The points where the skin felt itchy were marked and the five points were connected. Areas of alloknesis determined in this manner were copied to translucent papers for planimetry (2, 20). These measurements were performed in all study groups 5 min after histamine iontophoresis.

The theory of "auriculotherapy" is based on a hypothetical map in the shape of an inverted foetus showing different body regions represented on the external ear (17). Functional or pathological disturbances of determined body regions are said to be associated with increased electrical conductivity and increased tenderness of the corresponding specific ear areas. Evidence of this phenomenon was reported in several experimental studies (17, 21–23). According to Nogier, acute disturbances within a body site can be treated at the corresponding site in the hypothetical map (17). Clarifying this subject is another goal of this study. Electrical devices were developed and clinically tested for skin resistance measurements (23). The electro-acupuncture device (Fa. Medisana, Meckenheim, Germany) in our study locates increased electrical conductivity and increased tenderness of the expressed ear acupuncture points by giving an acoustic signal. Due to the standard method of irritation, the same combination of points must be expressed and located in all subjects. After identifying the ear acupuncture points the device stimulates these areas with a frequency of 50 Hz over 20 s. At several intervals after this procedure or without this procedure, alloknesis areas referring to ipsilateral or contralateral ear sides were determined to clarify the therapeutic effects.

Ear acupuncture

By acoustic signals of the electro-acupuncture hand-tool the following standardized ear acupuncture points could be located in all volunteers:

- The point on the latero-anterior helix, representing hypothetically the sensitive spinal cord of the forearm region.
- The somatotopic point of the lower arm skin at the anthelix.
- The reflection point of the spinal cord dorsal root.
- The thalamic point of oversensitive pain.

These four points, corresponding to the pathogenic stimulus on the volar forearm side, are derived from classical ear acupuncture charts. Subsequently, all four points were stimulated, as described above, for therapy (Fig. 1).

Experiments

With acupuncture treatment/Experiment 1 III (*Fig. 2*). After randomization using a computer-generated randomization list, 16 subjects were treated with left ear acupuncture and the other 16 with right ear acupuncture to clarify the effects of laterality. Five minutes after ear acupuncture alloknesis areas of the treated ipsilateral ($n = 32$) and the untreated contralateral ($n = 32$) volar forearm sides of the experimental groups were measured and compared with their respective same-sided controls.

Without acupuncture treatment/Experiment 1 II and Experiment 2 II & III (*Fig. 2*). Areas of alloknesis of the right (n=32) and left (n=32) volar forearm sides in experiment 1 were measured immediately prior to acupuncture treatment at 5 min after histamine iontophoresis and 5 min after acupuncture, as mentioned (Fig. 2). In a second assessment 2 weeks later the same subjects received histamine iontophoresis once more (experiment 2). Areas of alloknesis of the right (n =32) and left (n =32) volar forearm sides were measured 5 min and 10 min after histamine iontophoresis (Fig. 2). To detect differences in areas of allok-

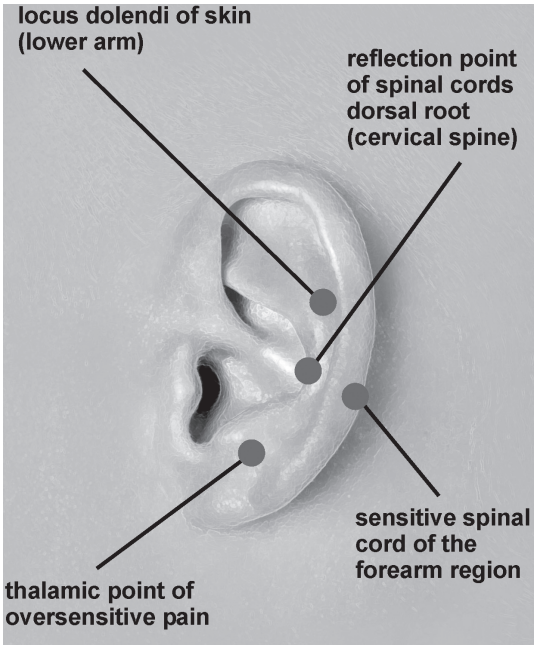

Fig. 1. Expressed and stimulated ear points.

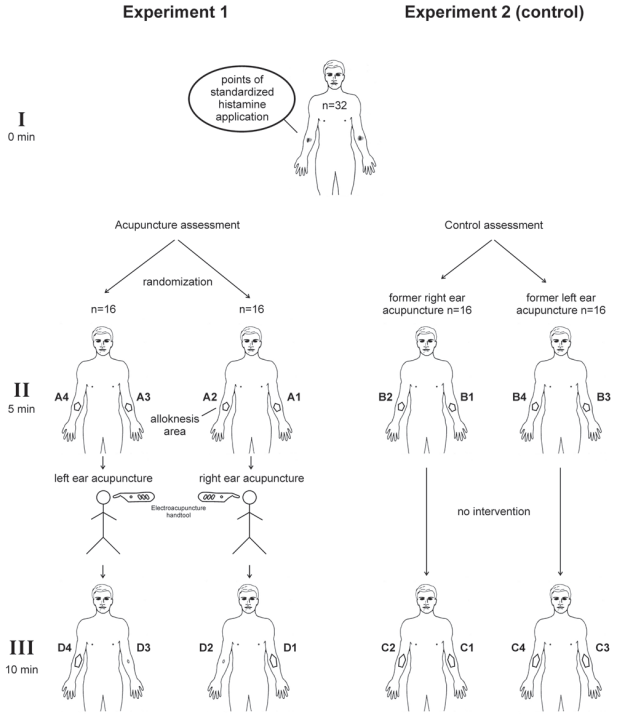

Fig. 2. The course of both experiments on 32 subjects. Experiment 2 was undertaken two weeks after experiment 1. A1 to D4 define absolute values of alloknesis areas, which are determined relating to a certain time, acupuncture side and experiment. Symbols in exp. 1 (II–III) denote intervention with electroacupuncture hand tools.

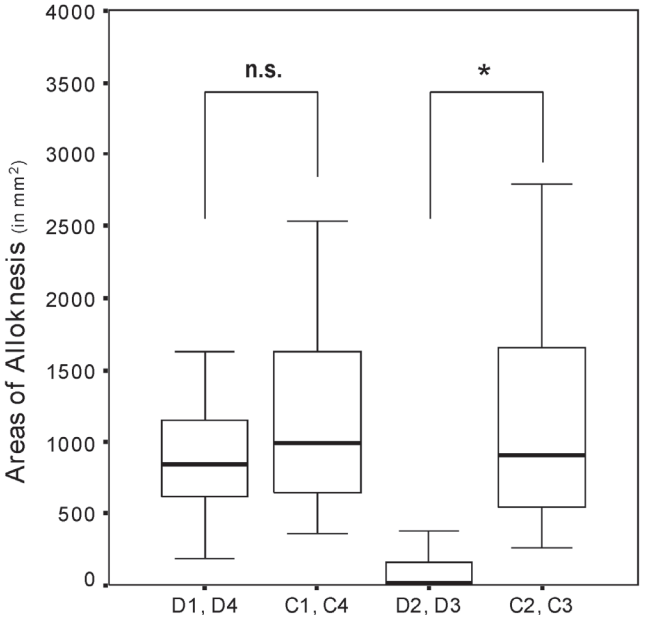

Fig. 3. Absolute values of the areas of alloknesis measured 10 min after histamine stimulus are compared between experiment 1 and experiment 2 (control). Ratio of alloknesis areas contralateral to acupuncture side in experiment 1 (D1,D4/C1,C4) and ratio of alloknesis areas ipsilateral to acupuncture side in experiment 1 (D2,D3/C2,C3) are illustrated. The box extends from the 25th percentile to the 75th percentile with a horizontal line at the median value (50th percentile); whiskers extend from the minimum value to the maximum value. n.s. not significant, * p <0.05.

nesis between right and left volar forearm sides we chose to compare the right and left sides separately. To detect differences in areas of alloknesis between experiment 1 and experiment 2 we chose to compare ipsilateral and contralateral forearm sides with reference to time and sides of both assessments.

Statistical evaluation

Data acquisition was performed using Excel (Microsoft, USA). Statistical analyses were performed with SPSS 10.0 (SPSS Inc., USA). After plotting the data of the variables in histograms and after Kolmogorov-Smirnov-test (p =0.001) it was concluded that a normal distribution could not be assumed (data not shown). As comparisons were always done pairwise, Wilcoxon paired samples test was used in all cases for statistical evaluation. Levels of p<0.05 were considered to be significant. All outcomes are given as median and range (minimum to maximum).

RESULTS

Alloknesis with acupuncture

Five minutes after acupuncture, the ipsilateral-to-treatment alloknesis area sizes of the forearms D2,D3 (median 21 mm^2) were significantly smaller (p <0.05) than those contralateral-to-treatment D1,D4 (median 851 mm^2) (See Fig. 2 for explanation of area designation). Six of 32 volunteers did not develop any alloknesis in ipsilateral forearms; 4 of them perceived itch only after mechanical stimulation at several separate points so that no discrete area could be determined. Contralateral-to-acupuncture area sizes after 10 min did not differ significantly between acupuncture D1, D4 and control C1, C4 assessment (p ≥0.05), whereas ipsilateral-to-acupuncture area sizes after 10 min were significantly reduced in acupuncture D2, D3 compared with control C2, C3 assessment (p <0.05) (Fig. 3).

Alloknesis without acupuncture

Without acupuncture therapy, there were no statistically significant differences in the comparison of areas of alloknesis of the right and left volar forearms with reference to time. Accordingly subjects in experiment 1 showed 5 min after histamine iontophoresis prior to acupuncture no differences in alloknesis areas (Exp 1/II in Fig. 2; Exp1/5min in Table I). Subjects in experiment 2 showed 5 min after iontophoresis (Exp 2/II in Fig. 2; Exp2/5min in Table I) and 10 min after iontophoresis (Exp 2/III in Fig. 2; Exp 2/10min in Table I) no statistical differences between right and left forearm alloknesis areas. The increase in size of alloknesis areas between 5 and 10 min after histamine was remarkable.

Area of alloknesis and acupuncture side

Wilcoxon test revealed no significant differences between right and left ear treated subjects and outcome (p ≥0.05).

Table I. *Experiments without acupuncture treatment. Comparison of values of alloknesis areas between left and right volar forearm sides. No significant differences were found between left and right volar forearm.*

Experiment/ Time[a]	L volar forearm, *n*=32/ R volar forearm, *n*=32	Median (Range) (mm^2)
Exp 1/5 min	A1,A3/A2,A4	440 (35–2035)/280 (21–3959)
Exp 2/5 min	B1,B3/B2,B4	263 (23–1897)/239 (20–2621)
Exp 2/10 min	C1,C3/C2,C4	969 (256–3912)/956 (272–5011)

[a]Time after histamine iontophoresis
L: left; R: right

DISCUSSION

Among several therapeutic procedures, acupuncture is proposed as a treatment for itch (24). Previous attempts to investigate the effects of acupuncture have been quite difficult and many trials were carried out to formulate a methodology for the assessment of acupuncture effectiveness (12). Difficulties were encountered in establishing an equal pathogenic stimulus in all study subjects, in defining a treatment protocol for all patients and in selecting an objective measurement of therapeutic outcome. With the model of experimentally induced itch and treating predefined acupuncture points, two previous studies overcame the first two problems. Outcome was measured with itch scales, such as maximal itch intensity and total itch index, which were subjectively described by the patient (10, 11).

The purpose of this study was to establish a reliable model to evaluate objectively the effects of electrical ear acupuncture. After inducing a similar pathogenesis among all study subjects with histamine iontophoresis, they were treated with electrical acupuncture of the same ear points. Outcomes were successfully measured by analysing the sizes of areas of alloknesis.

The most important results of the present study are:

- All patients showed expression of the expected somatotopic ear points that were first detected by an acoustic signal and subsequently treated among all volunteers.
- Demonstration of diminished or undetectable areas of alloknesis after ear acupuncture at the forearm ipsilateral to treatment.
- Undiminished development of areas of alloknesis after ear acupuncture at the forearm contralateral to treatment.
- Increasing areas of alloknesis due to histamine iontophoresis in the absence of acupuncture.
- No difference in outcome between right and left ear acupuncture.

Heyer et al. (2) observed increasing size of areas of alloknesis during the first 15 min after histamine application, similar to our findings, in forearm sides not connected with ipsilateral treatment or areas of alloknesis of the control assessment. Patients receiving acupuncture exhibited significantly smaller areas; only observable at a few points and/or totally disappearing 5 min after treatment. Therapeutic outcome on ipsilateral forearm was independent of which ear was acupunctured.

Comparable results on experimentally induced alloknesis were achieved with topical application of antihistamines or local anaesthetics (25). Significantly reduced areas of alloknesis and wheal flares were also reported after cetirizine and naltrexone in experimentally evoked itch (26). In contrast, neither cutaneous field stimulation nor transcutaneous nerve stimulation resulted in any significant effect upon alloknesis in chronic itch. Therefore altered sensory processing in chronic itch patients as compared with healthy people has seemed worthy of discussion (12).

The effect of naltrexone upon acetylcholine-induced alloknesis in patients with atopic eczema suggests central inhibition rather than a blockade of nociceptors in the periphery (27). Morphine derivates may inhibit the excitation of itch-mediating central neurones and reduce alloknesis. Studies on electro-acupuncture have revealed that endogenous opioids play an essential role in mediating these effects. Higher release of encephalin, beta-endorphin and dynorphin in the central nervous system has been reported (28). Endogenous opioids released after acupuncture may play a role by inhibiting the central excitation of neurones that causes alloknesis reaction after mechanical stimulus. A study with experimental capsaicin-induced inflammation in rats showed reduced effects of acupuncture with intraperitoneal co-administration of naloxone (29). Endogenous opioids released after acupuncture may play a role by inhibiting the central excitation of neurones that are involved in itch and alloknesis perception.

Although this study concentrated on the effects of single ear acupuncture on alloknesis reaction and not on histamine flares or itch perception, a former investigation had observed significantly smaller maximal flares when receiving acupuncture instead of pseudo-acupuncture or no intervention (11). Up to now, there has been no study evaluating the effects of serial acupuncture on histamine responses or itch in a standardized objective model. As mentioned previously, ear acupuncture has faster and, at least initially, more intensive effects compared with serial body acupuncture. Therefore, ear acupuncture is to be preferred for installing an acupuncture model. Acute disorders such as histamine iontophoresis are a domain of ear acupuncture, although serial ear acupuncture might be better suited to combat chronic itch, as it is shown in several clinical trials and therapy regimes (30). An anti-histamine effect of serial acupuncture is described and might cause reduced itch reaction as well as reduced histamine-induced bronchial spasms in anaphylactic asthma. Furthermore, decreased IgE and eosinophilic granulocyte levels were found after therapy with serial acupuncture (31, 32).

In summary, our model objectively demonstrates the effectiveness of ear electro-acupuncture in contrast to the results of earlier subjective studies. Ear electro-acupuncture appears to reduce alloknesis in experimentally-induced itch. Laterality of therapy is essential for acupuncture effects. Acupuncture may be a therapeutic alternative with a very low risk-to-benefit-ratio in itch.

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