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Cholinergic and Adrenergic Sweating in Atopic Dermatitis

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Sweating responses to methacholine and adrenaline were compared with an evaporimeter in normal-looking back and forearm skin from patients with atopic dermatitis (AD) and from non-atopic controls (NA). With both stimulants, the sweat rates were higher in forearm than in back skin in both groups, and between the two sites the rates showed positive correlations which were statistically significant in both groups. With methacholine the responses were slightly depressed in both areas in AD. With a low suprathreshold adrenaline concentration (5×10^{-6} mol/l) the responses were equal in both groups but a tenfold higher adrenaline concentration elicited an increase of 55% in sweating rates in the back skin of NA and a 15% depression in the back skin of AD subjects ($p < 0.05$). On arm skin there was a similar trend, but less marked. Between the cholinergic and adrenergic sweating responses a positive correlation was found on arm skin in AD, suggesting that the unknown mechanism of sweat depression in AD might be the same for both drugs. ***Key word: Sweat stimulation.***

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In 1953 Lobitz & Campbell (1) found normal sweating responses to both cholinergic and adrenergic stimulation in subjects with atopic dermatitis (AD). In that study they used a non-controlled qualitative imprint technique. Subsequently, quantitative studies have been performed on forearm skin and have shown in AD either increased (2, 3) or normal sweating responses (4) to cholinergic stimulation. Investigations using adrenergic stimulation also gave varying results (5, 6).

Our recent results revealed in back skin of AD subjects depressed sweat responses to methacholine (MCH) (7, 8). Since quantitative studies comparing the cholinergic and adrenergic sweat stimulation in AD are lacking, MCH-induced and adrenaline-induced sweating responses in this study were compared in back and forearm skin in AD and non-atopic subjects (NA), by means of evaporimetry. The suitability of this technique for these purposes has previously been proven and the MCH concentration (5×10^{-7} mol/l) was best suited for routine sweat stimulation (9).

MATERIALS AND METHODS

Subjects

The subjects (mean age 20.6 years) were young males from the Central Military Hospital, Helsinki. Informed consent was obtained from all participants. The atopics had mild or moderate AD (10) without or with allergic rhinitis. All topical therapy had been interrupted at least 3 days previously and peroral or nasal medication one week prior to sweat tests. Phototherapy or suntanning less than one month prior to testing was a criterion for exclusion. The NA subjects were either healthy, had visited the outpatient ward for a suspected venereal disease, or they had a minor non-atopic dermatosis.

Test procedure

Tests were carried out on clinically normal-looking back and/or forearm skin during a winter season under normal laboratory conditions (mean room temperature 23.1°C, mean RH 28%). The subjects rested quietly supine with the upper body unclothed. After a 20 min adaptation period, baseline water loss (BWL) and skin temperature at the test sites were measured (Exacon thermometer, Exacon Scientific Instruments, Taastrup, Denmark). Methacholine chloride (Mecholyl, Sigma) or adrenaline were given intracutaneously in 0.1 ml volumes using 27-gauge needles (9).

The rate of BWL and, after sweat stimulation, the peak evaporation rate of total cutaneous water loss (CWL) were recorded with an evaporimeter (Evaporimeter EP 1, ServoMed, Stockholm, Sweden) (11). The pure sweat loss rate (SL) was calculated by subtracting BWL from the corresponding CWL value. In this study the term BWL was preferred instead of the term transepidermal water loss (TEWL) because the sweat gland function was not inhibited by an anticholinergic drug (12). The potential sweating component (resting sweat) in BWL could increase the amount of TEWL and the level of total cutaneous water loss (CWL) but was not considered to affect the SL level. All water loss data were expressed as g/m^2h.

Series 1. MCH-induced sweating responses were compared on forearm and back skin in 34 AD and 38 NA subjects with the standard suprathreshold concentration 5×10^{-7} mol/l.

Series 2. Sweat responses to two different adrenaline concentrations were examined in back and forearm skin. Using a suprathreshold concentration of 5×10^{-6} mol/l, comparisons were made in 31 AD and in 32 NA subjects, and at tenfold higher concentration in 22 AD and 22 NA control subjects.

Series 3. Sweat responses to both adrenaline and MCH suprathreshold concentrations in the same individual were conducted in symmetrical contralateral skin areas, either on the back (AD, $n = 20$; NA, $n = 27$), or both back and forearm (AD, $n = 18$; NA, $n = 18$). The subjects were also included in series 1 and 2.

Statistics

The Wilcoxon rank sum test was used to compare the sweat responses in AD and NA groups and Wilcoxon matched-pairs signed-ranks test for comparison of sweat responses of back and forearm skin in both groups. Correlations were calculated with the Spearman rank correlation test.

RESULTS

Series 1

Fig. 1 presents the MCH-induced median SL values. The SL level in forearm skin in AD was 44% higher and in NA, 22% higher than for the back skin. There was a tendency toward lower SL values in AD than in NA in both areas. The difference between the groups was not significant in either back or forearm skin. Between individual SL values the correlations in

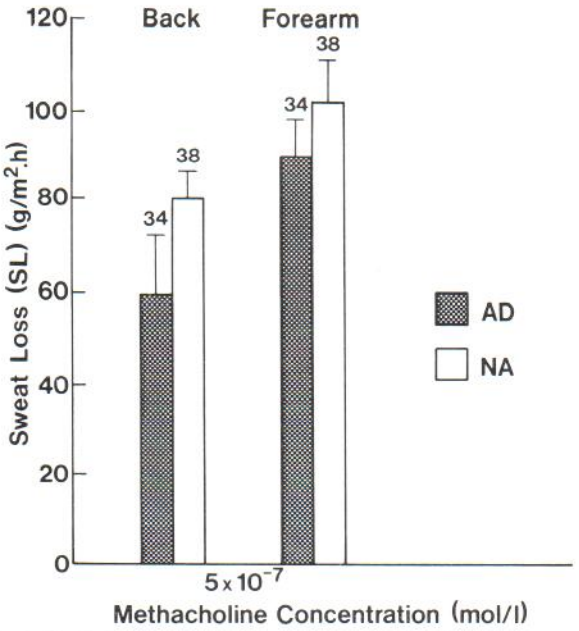

Fig. 1. Methacholine-induced sweating responses (Median ± SE(M)) in back and forearm skin from patients with AD and in non-atopic controls. SE(M) = standard error of median.

back vs. forearm skin were significant both in AD ($r = 0.51$, $p < 0.005$) and in NA ($r = 0.77$, $p < 0.001$).

Series 2

Fig. 2 presents the back and forearm responses to two adrenaline concentrations. With adrenaline 5×10^{-6} mol/l the median SL level in the AD group was 130% higher ($p < 0.001$) in the forearm than in the back skin and 81% ($p < 0.001$) higher in the NA group, respectively. With this concentration there were no significant differences between the groups. With a tenfold higher concentration there was a 15% decrease in SL values in AD back skin and a 56% increase in NA back skin. The difference in responses between AD and NA was significant ($p < 0.05$). In forearm skin the decrease in AD was 27% and the increase in NA 15%.

Correlations between back and forearm skin sweat responses with these two concentrations were, in AD group: $r = 0.72$ ($p < 0.001$) and $r = 0.94$ ($p < 0.001$), and in the NA group: $r = 0.68$ ($p < 0.001$) and $r = 0.47$ ($p < 0.05$).

Series 3

In AD patients tested with MCH (5×10^{-7} mol/l) and adrenaline (5×10^{-6} mol/l) the correlation of SL levels in back skin was 0.31 and in forearm skin, 0.47 ($p < 0.05$). In the NA group the corresponding correlations were 0.42 and 0.26. In both groups the adrenaline-induced sweating responses were 30% to 40% of the response obtained with MCH.

The mean BWL levels and skin temperatures in AD and NA back skin were 9.1 ± 2.0 g/m²h (33.2°C) and 8.6 ± 2.8 g/m²h (33.1°C). The corresponding values in AD and NA forearm skin were 8.7 ± 3.0 g/m²h (32.6°C) and 8.0 ± 1.7 g/m²h (32.2°C). No significant differences in BWL levels nor in skin temperatures between the groups were found.

DISCUSSION

Warndorff (3) and Kaliner (13), reporting increased cholinergic sweating responses on arm skin in AD (3) and respiratory atopy (3, 13), proposed that their findings were consistent with Szentivanyi's concept (14) of cholinergic hypersensitivity due to an inadequate beta-adrenergic regulatory control.

In contrast to these observations we found lowered cholinergic sweating responses in the back skin of AD subjects and normal responses in respiratory atopics (7). These contradictory results might have been explained by regional differences, since hypohidrosis on one area may lead to compensatory hyperhidrosis on other area. However, in this study, no hyperhidrosis was found on AD forearm skin. Rather, the present and the preliminary findings (15) are in agreement with those obtained by Murphy et al. (4) who, using acetylcholine stimulation, found no increase in the numbers of activated sweat glands on arm skin of AD patients.

According to our previous results the sweating response to MCH was more significantly lowered in dry-looking AD skin than in normal-looking AD skin (7). In this study the hypohidrotic trend on normal-looking AD skin was similar in both back and forearm skin, though the differences did not reach the level of statistical significance.

The physiological significance of adrenergic sweating is not adequately understood. Opinions on the existence of periglandular adrenergic nerves are divided (16, 17, 18) and the coupling of adrenergic and cholinergic stimulus-secretion is not yet clear (19, 20). The demonstration of several neuropeptides around the sweat glands (21, 22) and some neuropeptides also over the membranes of secretory cells within the eccrine sweat glands (22) may in the near future give more information about the complex nervous control of eccrine sweating.

At the lower concentration of adrenaline (5×10^{-6} mol/l)

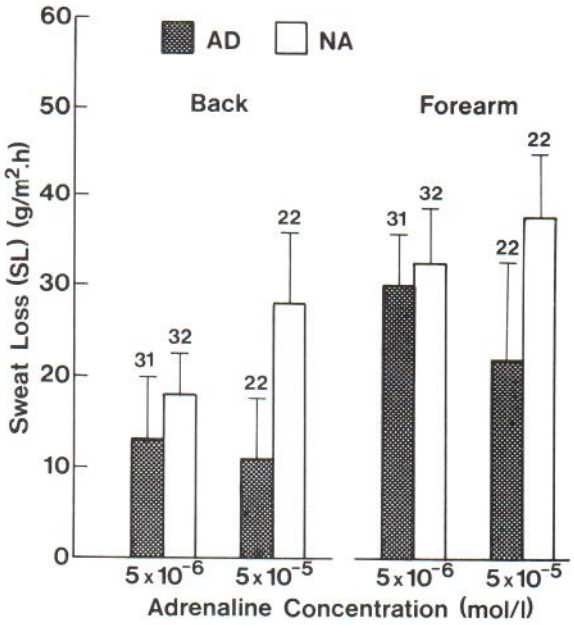

Fig. 2. Sweating responses (Medians ± SE(M)) to adrenaline concentrations 5×10^{-6} mol/l and 5×10^{-5} mol/l in back and forearm skin in AD and in NA.

the sweating responses in AD and NA subjects were fairly equal. As expected, the responses increased significantly in NA subjects with the tenfold higher concentration, particularly on the back skin. In AD subjects, no increase occurred at the higher concentration; rather, there was a slight depression in both areas. Also Warndorff & Neefs (5) found a lowered sweating response to adrenaline in forearm skin in 8/10 patients with an atopic disposition, compared with 6/16 in other non-ichthyotic dermatological subjects, whereas Thune & Kocsis (6) observed depressed values in AD patients only in the autumn.

Adrenaline possesses alpha- and betalmimetic activity. Reports on sweating responses induced by alpha- and beta-adrenoceptor agonists have been contradictory (19, 20). Warndorff & Hamer (23) noted increased sweating responses to the non-selective beta-agonist isoprenaline in atopic subjects. On the other hand, Sato & Sato (24) found a normal response to the same stimulant in one patient with generalized AD.

The reason for a weaker adrenaline response in the AD group may not be related to the extent of vasoconstriction, since no difference was found in adrenaline-induced vasoconstriction curves or skin temperatures in AD patients vis-à-vis non-atopics (25).

On the other hand Hörnqvist et al. (26) found in AD – especially in summer – a significantly increased sensitivity of dermal vessels to blanching in response to the $alpha_1$-agonist phenylephrine and also to the beta-agonist isoproterenol, especially in winter.

The reasons for the cholinergic and adrenergic sweating disturbances in AD observed in this study are not clear. In both subject groups the adrenergic sweating response was about 30% in back and about 40% in forearm skin of the corresponding cholinergic suprathreshold response. Sato & Sato, using maximum drug concentrations, found that the responses to adrenaline were approximately one-tenth of that evoked by an identical dose of MCH (24). There was a positive correlation between the individual responses to MCH and adrenaline on the forearm skin of AD subjects. In this group there were subjects demonstrating low sweat responses to both MCH and adrenaline. This suggested that the mechanism of sweat disturbances for both drugs was the same. Unfortunately, individual comparisons were only performed with the low suprathreshold concentration.

In conclusion, cholinergic hyperreactivity could not be demonstrated in AD skin. Rather, there was a tendency to hypohidrosis. With a low adrenaline concentration, no sweating disturbance was observed in AD, but at a higher adrenaline concentration, a tendency to hypohidrosis was observed, particularly on back skin.

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