Generation and transit pathway of H^+ is critical for inhibition of palmar sweating by iontophoresis in water

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SATO, KENZO, DAVID E. TIMM, FUSAKO SATO, ERIC A. TEMPLETON, DIMETRIUS S. MELETIOU, TAKASHI TOYOMOTO, GYULA SOOS, AND SHORGE K. SATO. *Generation and transit pathway of H^+ is critical for inhibition of palmar sweating by iontophoresis in water.* J. Appl. Physiol. 75(5): 2258–2264, 1993.—Passing galvanic current across the skin (known as "tap water iontophoresis" or TWI) inhibits sweating; however, its mechanism of action is unclear. Using improved methods, we confirmed that anodal current has more of an inhibitory effect than cathodal current, water is superior to saline, and the inhibitory effect is a function of the amperage used. To address the importance of current flowing through the pores, a layer of silicone grease was placed on the skin to reduce the shunt pathway across the epidermis. With silicone, total skin conductance decreased 60% without the sweat pores being occluded, swelling of the stratum corneum and collapse of the poral lumen was prevented, and current-induced inhibition of sweating was enhanced, most likely because of an increase in current density in the pores. The pH of anodal water, but not of saline, dropped to 3, whereas that of cathodal water increased to 10 during passage of current through the skin. Acidified anodal water was superior to alkaline water. Sweat glands isolated from TWI-induced anhidrotic palmar skin responded to methacholine in vitro, but the sweat rate and pharmacological sensitivity were slightly lowered. Thus the strong acidity generated by hydrolysis of water in the anodal bath and the further accumulation of H^+ in the sweat duct by anodal current may be responsible for TWI-induced inhibition of sweating due to an unknown lesion(s) in the duct or sweat pore. The secretory coil function may also be altered because of exposure to intense acidity during TWI. The importance of H^+ movement into the sweat pore for inhibition of sweating could be further exploited to develop new strategies for the control of sweating.

sweat gland; hyperhidrosis; iontophoresis; galvanic current

EXCESSIVE SWEATING (hyperhidrosis) of the palms and soles is an emotionally, socially, and occupationally distressing and debilitating condition. The control of excessive sweating in this and other clinical conditions has long been a major challenge for clinicians and physiologists. Passage of galvanic current through the skin of the hands or feet in water (so-called "tap water iontophoresis" or TWI) (1, 6, 13, 15)[1] has been used to successfully control excessive sweating (3) in 84–87% of subjects (4, 7, 14).

TWI was discovered almost 50 years ago. Takata (15) observed in 1942 that passing anodal (positive) current through the skin in water completely inhibited sweating after a latent period of a few days. Shelley et al. (13), unaware of Takata's work, reported in 1948 on the fundamental characteristics of galvanic current-induced anhidrosis in the skin of the back. For example, by visualizing sweat droplets with quinazarine powder, they observed that sweating was inhibited only under the anodal electrode, distilled water was superior to saline as an anodal medium, the degree of induced anhidrosis was a function of the amperage used, and sweat retention developed in the treated skin when the subjects were placed in a sauna. Shelley et al. thus hypothesized that the anodal galvanic current inflicted a nonspecific injury to the epidermis, causing abnormal keratinization of the poral epithelium and thus keratinous plugging of the pores. It is unknown, however, whether Shelley's observations on the back can be readily extrapolated to palmar sweating. For example, a variety of methods that can easily induce anhidrosis in nonpalmar skin (2, 13) are ineffective on the palms and soles. Furthermore, on the back, a single TWI treatment is sufficient to induce anhidrosis (13, 15), and clinical and histopathological evidence of poral plugging and sweat retention can be observed (13). In the palm, however, multiple treatments are required to inhibit sweating and no clinical or histopathological evidence of poral plugging or tissue injuries has been observed (3, 14).

Very few basic studies have been published on the mechanisms of current-induced inhibition of sweating over the past 50 years. In the present study, we reexamined some of the reported features of this phenomenon using an improved methodology. Namely, why is water superior to saline? Why is the anode more effective than the cathode? What is the route of the current (i.e., sweat pore vs. epidermis) that is instrumental in inducing anhidrosis? Are the functions of the secretory coil also altered by TWI? It is hoped that this study will provide further understanding on the mechanism of sweating and help develop new strategies to control excessive sweating.

MATERIALS AND METHODS

Materials. A Fisher MD-1 galvanic power supply was purchased from Fisher (Glendale, CA). For most experiments that involved finger tips, simple power supplies were constructed using 10 9-V transistor batteries connected in series, 20-kΩ rheostats, ammeters, and pilot

[1] Tap water is an inexpensive, practical alternative to distilled water and is widely used in clinical settings. Shelley et al. (13) originally used distilled water.

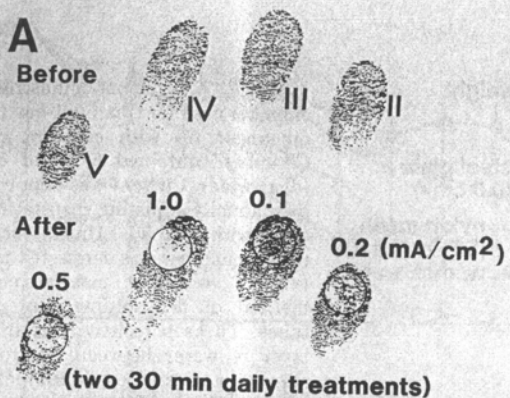

FIG. 1. Determination of active sweat pores. *A*: example of response to daily treatment with 4 different amperages: 0.1, 0.2, 0.5, and 1.0 mA/cm^2. Iodine-impregnated paper was used to visualize treated areas and adjacent control sites. Roman numerals, number of finger. This subject showed most dramatic responses, especially to 1.0 mA/cm^2 (see 4th finger). Before, before treatment; After, taken on *day 3* (24 h after 2nd treatment). *B*: illustrative photograph of Silastic imprints used for counting active pores. Note numerous beads of sweat along cutaneous ridges (3 sweat droplets are marked with arrows).

lamps. Elasticon used for obtaining silicone rubber imprints of finger tips was obtained from Kerr (Romulus, MI). The electrolytic water vapor analyzer was purchased from Meeco (Warrington, PA). A Keithley (Cleveland, OH) 602 electrometer was used to calibrate all ammeters used. High-vacuum silicone grease was purchased from Dow Corning (Midland, MI). All other reagents were obtained from Sigma Chemical (St. Louis, MO), unless otherwise noted.

Experimental subjects. Subjects (18 men, ages 16–25, and 6 women, ages 18–24) were recruited from patients who visited the Dermatology Clinic of the University of Iowa Hospitals for severe palmar hyperhidrosis or were selected from those who responded to ads posted on the University campus and proved to have severe palmar hyperhidrosis during the period 1984–1992. The subjects had not treated their hands for at least 6 mo before the study. The experimental protocols were approved by the institutional Human Subject Committee, and informed consent was obtained from each subject before the study.

Determination of active sweat pores on the finger. Iodinated paper (100 sheets of white photocopy paper equilibrated with 1 g of iodine crystals for ≥2 wk in an airtight jar; see Ref. 12) was used for obtaining preliminary sweat imprints from the pulp of the fingers for screening purposes before each iontophoretic treatment (Fig. 1*A*). Silastic imprints were then taken (Fig. 1*B*). A stencil with a 0.04-cm^2 hole was placed over the Silastic imprints, and the number of pores from five different areas inside the 1-cm^2 test site was counted under a stereomicroscope and averaged. Because sweating in the palms and soles changes drastically from moment to moment, strong emotional stimuli were applied while the Silastic imprints were taken, e.g., having the subjects take a quiz or do mental arithmetic problems or pinching their skin with forceps while they sit with their eyes closed. The response to treatment was always expressed by the ratio of active pores inside the test site relative to those outside the test site in each imprint.

Treatment of finger tips by TWI. To minimize the effect of oil or sebum present on the skin, the finger tips were washed for a few seconds with a soap bar, rinsed thoroughly with tap water, and dried with a hair dryer. Special chambers (Fig. 2*A;* area of 1 cm^2 and volume of 5 cm^3) were constructed to pass constant current through the 1-cm^2 test sites on the finger tips. The side arm of the chamber allowed water to move freely as the finger tip was placed on the chamber. The (house) distilled water supplied by the university's central facility through a water pipe and faucet was used (contaminants were <3 ppm). Tap water (see footnote 1), which was used in the preliminary study with equal success (16) and is widely used for treatment of patients in clinical settings, was not used for the present study because its composition (pH and purity) changes daily and seasonally. The 1-cm^2 test site was marked by four small dots of silver nitrate placed immediately outside the circular rim (see Fig. 1), which produces durable dark dots on exposure to light. Except for the study of amperage vs. response, the finger tips were coated with silicone grease unless otherwise noted. The indifferent electrode (cathode) was a steel plate immersed in a tray of saline. A sheet of sponge, ~1 cm thick (Fig. 2), was placed between the subject's foot and the steel plate. The test sites were treated with 0.2 mA/cm^2 of anodal current (unless otherwise specified) for 30 min daily. Current was adjusted manually with a rheostat to keep the current level within ±5% of the predetermined level.

Determination of skin conductance. To measure the change in the total electrical conductance (the inverse of resistance) of the skin, the device shown in Fig. 2*B* was used. The setup is similar to Fig. 2*A* except that the amount of water between the skin and the electrode (note the water layer is a major source of variability in the total resistance) was kept at a thickness of 50 μm by using a nylon mesh under a constant 70 g of pressure. Specific skin conductance (C_s) is the inverse of specific resistance (R_s, expressed in $\Omega \cdot cm^2$), which was calculated from the amount of current (I) when 10 V was applied to the circuit minus 1.3 kΩ for the average resistance arising from the foot (determined in separate experiments) and modified for the test site area of 0.5 cm^2. The formula is $C_s = (1/R_s) = 1/[0.5(10 - 1{,}300I)]$ $(\Omega^{-1} \cdot cm^{-1})$.

Because the total resistance was in the range of 40–100 kΩ, most of the resistance was derived from the test site on the finger. Between resistance measurements, the fingers with or without silicone coating were immersed in water and the electrode was rinsed in distilled water to remove any contaminating electrolytes in the mesh.

Determination of sweating by moisture vapor analysis.

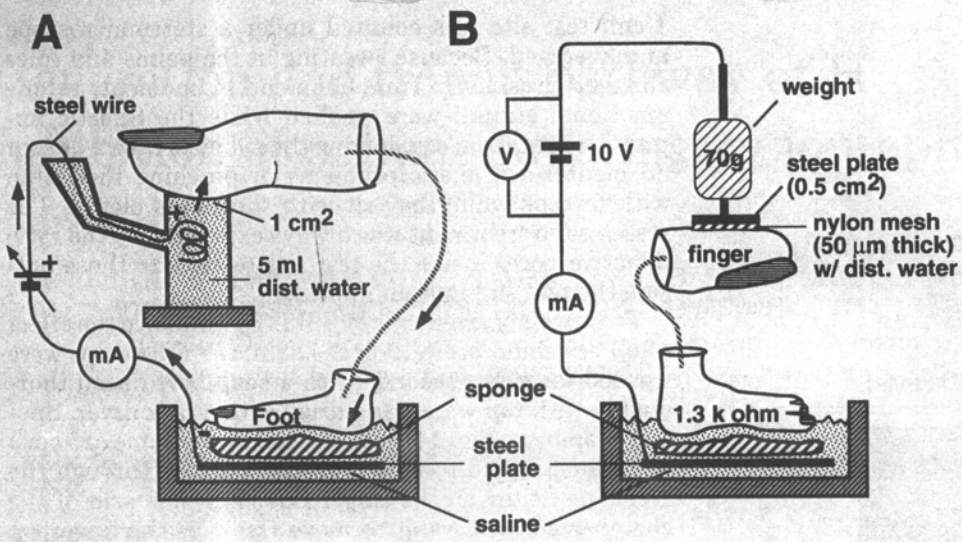

FIG. 2. *A*: schematic illustration of chamber used for treating 1-cm² test site on finger tip with constant current. Chamber contained 5 ml of distilled (dist) water. Current was kept constant by manually adjusting rheostat (battery sign with arrow). Unless otherwise noted, chamber was connected to anode (+). V, voltmeter; mA, ammeter. *B*: method of determining skin conductance. To keep resistivity arising from layer of water between electrode and skin constant and to a minimum, a piece of nylon mesh, 50 μm thick, was placed between skin and pressed with 70-g weight.

Two subjects who had skin biopsies performed on their palms also had their sweating rates in response to mental stimuli and intradermal methacholine (MCh) determined with a Meeco water vapor analyzer (12, 17). The quantification of sweating was intended to verify the complete inhibition of sweating by TWI for the biopsy and the subsequent in vitro study. Briefly, the rim of a capsule with an open sensing area of 0.28 cm^2 was coated with silicone grease. The capsule was placed on the thenar area of the palm and secured with tape. Dry nitrogen gas was continuously introduced at 100 ml/min into the capsule, and the moisture in the outflow nitrogen gas was continuously monitored by an electrolytic water vapor analyzer. The analyzer was calibrated as described previously (11).

Skin biopsy and sweat induction from isolated human sweat gland in vitro. The method of sweat induction in vitro has been previously described (9, 10, 12). In two volunteers, the entire palm of one hand was treated by TWI to near anhidrosis while the other palm was left untreated. Elliptical pieces of skin, 7 × 3 mm, were surgically excised under local anesthesia of lidocaine with epinephrine from the thenar prominences near the center of the palm: one from the treated palm and another from the symmetrical site of the untreated palm. The excised tissue was blotted of blood, sliced into several pieces, and immediately washed in several changes of cold (~10°C) modified Krebs-Ringer bicarbonate solution containing (in mM) 125 NaCl, 5 KCl, 1.0 $MgCl_2$, 1.0 $CaCl_2$, 25 $NaHCO_3$, 1.2 NaH_2PO_4, and 5.5 glucose, as well as 20 mg/100 ml bovine serum albumin. The pH of this medium was 7.48 at 37°C when gassed with a mixture of 5% CO_2-95% O_2. Single sweat glands were isolated under a stereomicroscope with sharp forceps in a dissection chamber kept at 14°C. The sweat induction pipette was ~8 cm long, 2.5 mm in diameter at the shank, and 50 μm at the tip. Sweat samples were collected with an oil-filled inner (sampling) pipette usually every 10 min, and their volumes were calibrated.

RESULTS

Amperage vs. inhibition of sweating. The amperage-response relationship of anodal current-induced inhibition of sweating has never been studied in the palm. With the use of the method illustrated in Figs. 1*A* and 2*A*, four test sites were treated with four different amperages for 30 min daily. As shown in Fig. 3*A*, the reduction of active sweat pores was proportional to the amperage used, with 1 mA/cm^2 being the most effective. However, because the 15–25 mA/palm usually used clinically (1, 6, 13, 15) corresponds to 0.15–0.25 mA/cm^2 (assuming that the area of palmar skin including the sides of the fingers is ~100 cm^2), we mainly used 0.2 mA/cm^2 in the subsequent experiments.

Effect of pathways of current flow. One of the goals of the present study was to test the hypothesis that it is the current flow through the sweat pore, not the epidermis, that is important in inducing anhidrosis. We therefore applied a thin layer of silicone grease to the skin to insulate the epidermis between the pores, which would minimize the current flow through the epidermis and force more current to flow through the pores. Applying silicone grease to the skin does not occlude sweat pores. This has been shown by the presence of the same number of open pores in Silastic imprints or iodinated paper before and after the application of silicone grease (data not illustrated). We also observed, in uncoated skin, that the skin swelled during immersion in water and that the swelling of the skin itself occluded the sweat pores (this was convincingly shown in Silastic imprints; data not shown). In contrast, in the silicone-coated finger, skin swelling and poral occlusion were much less evident (data not shown). The skin conductance, as determined by the method shown in Fig. 2*B*, decreased to 40% of the control when the finger was silicone coated and remained constant over the 30 min of immersion in water ($n = 6$, $P < 0.001$; data not shown). In contrast, the skin conductance of the uncoated control finger skin increased over the initial 15 min of water immersion and plateaued thereafter (data not shown). The data are best interpreted to indicate that, in uncoated skin, ≤60% of the current traverses the epidermis and bypasses the sweat pores. The current across the epidermis may increase significantly with the time of water immersion because of increasing swelling of the skin and a narrowing of the poral diameter by hyperhydration of the stratum corneum. Thus it follows

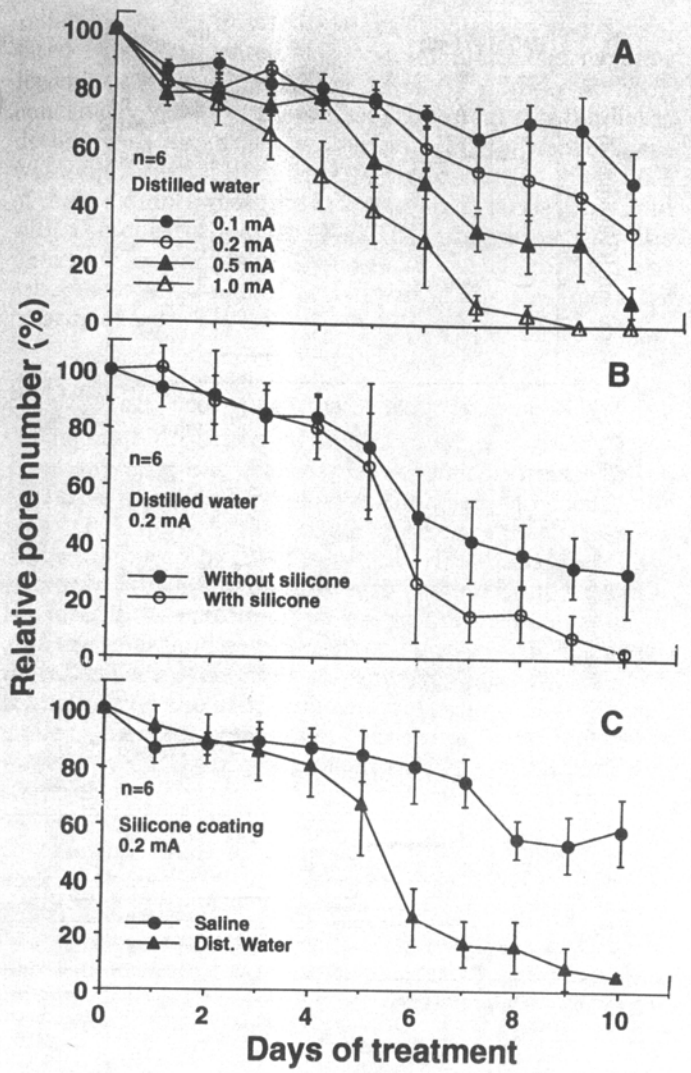

FIG. 3 *A*: amperage vs. galvanic current-induced inhibition of sweating on finger tips. Here and in Figs. 4 and 6, efficacy of inhibition is given as percentage of number of active pores in treated vs. adjacent untreated skin sites in each finger (each point is mean ± SE). Silastic sweat imprint was taken of each finger immediately before iontophoresis. Test sites were treated daily for 30 min. Distilled water was used as anodal medium. In this dose-response study, silicone coating was not used. *n*, No. of subjects used. *B*: effect of silicone coating on anodal current-induced inhibition of sweating. Distilled water was used for both groups. From *days 7* to *10*, difference between 2 groups was significant ($P < 0.05$). Test sites for only experimentals were coated with silicone and treated daily at 0.2 mA/cm^2. *C*: comparison between saline and distilled water as anodal medium. Test sites for both controls and experimentals were coated with silicone and treated daily at 0.2 mA/cm^2. Difference between saline and distilled water is significant ($P < 0.01$) from *days 6* to *10*.

that insulation of the epidermis more than doubles the amount of current flowing through the sweat pores.

Effect of silicone coating. As shown in Fig. 3*B*, silicone coating significantly ($P < 0.01$ for *days 7–10*) enhanced the efficacy of TWI so that 0.2 mA/cm^2 with silicone coating yielded an effect comparable to that achieved by 0.5 mA/cm^2 without silicone coating (Fig. 3*A*). This further supports the hypothesis that the current flow through the sweat pores is important for TWI-induced inhibition of sweating. Therefore, in the subsequent studies, silicone coating was used for both controls and experimentals.

Distilled water vs. saline and anode vs. cathode. It has been puzzling that water is superior to saline as an anodal medium and that the anode is more effective than the cathode in nonpalmar skin (13, 15). No similar observations have been reported in the skin of the palms or soles. The data in Fig. 3*C* show that distilled water was also far superior to saline in the palm, where saline could achieve only 35% inhibition of sweating by *day 10* vs. 89% for water (Fig. 3*C*). As shown in Fig. 4, the anode was significantly superior to the cathode at both 0.1 and 0.2 mA/cm^2. It should be noted, however, that even cathodal current at 0.2 mA/cm^2 exhibited some effect, as shown in the inhibition of sweating by as much as 60% after *day 10* in water with silicone coating of the skin.

pH of anodal and cathodal medium. The mechanism involved in the beneficial effect of the combination of anodal current and distilled water as the anodal medium (13, 15; see above) is totally unknown. It has been known for more than 100 years (5, 8) that when inert metals such as steel or platinum are used, voltage applied to the electrode forces the water in the reservoir to become the fuel for electrochemistry, i.e., the hydrolysis of water (8). This is in contrast to the Ag-$AgCl_2$ electrode, which transfers electrons by converting Ag to Ag^{2+} (such as $AgCl_2$). Hydrolysis of water causes the anodal medium to become more acidic and the cathodal medium to become more alkaline. However, the extent to which acidification proceeds in the anodal medium during TWI remained to be studied. As shown in Fig. 5, when the pH of the me-

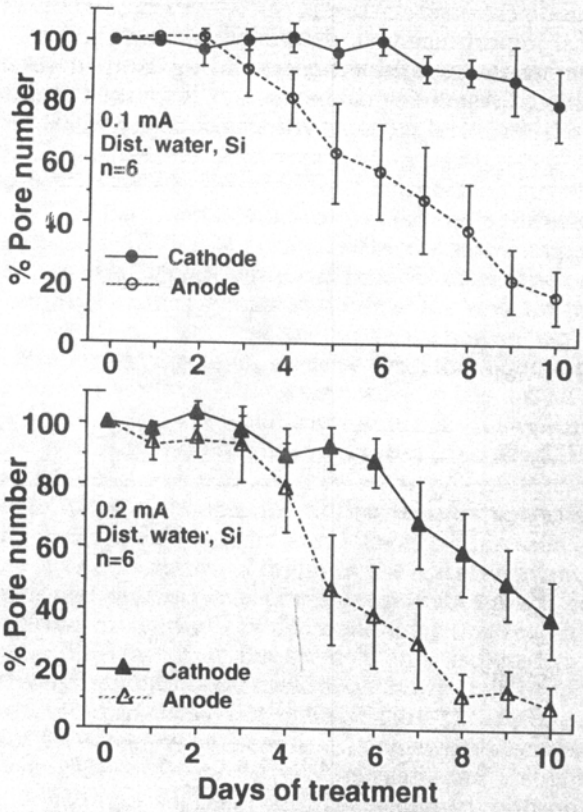

FIG. 4. Comparison between anodal and cathodal current. Test sites for both controls and experimentals were coated with silicone (Si). Anodal and cathodal currents were compared at 0.1 mA/cm^2 (*top*) and 0.2 mA/cm^2 (*bottom*). Difference between anode and cathode was significant ($P < 0.01$) from *day 6* to *day 10*.

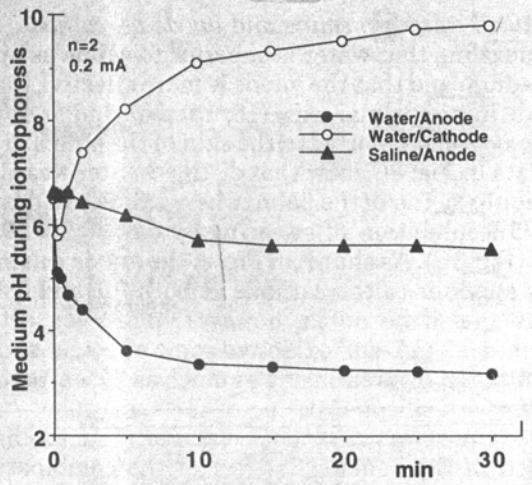

FIG. 5. Change in pH in anodal and cathodal reservoirs during iontophoresis. Chamber shown in Fig. 2*A* was used. Test sites were coated with silicone and treated at 0.2 mA/cm^2. Before pH was measured with a glass pH electrode (4-mm-diam tip), medium was mixed well. Current was reversed when cathodal pH was determined. Note that chamber contained 5 ml of medium for 1 cm^2 of skin, which is equivalent to 500 ml of tap (or distilled) water normally used in a tray for treatment of hyperhidrosis in a clinical setting.

dium was directly determined with a glass pH electrode during iontophoresis with the chamber shown in Fig. 2*A*, the pH in the anodal reservoir dropped to as low as 3, whereas the pH in the cathodal reservoir approached 10. Interestingly, when saline was used in the anodal reservoir, the pH change was minimal (Fig. 5). It is possible to speculate that the acidic pH of the anodal medium is of critical importance for inhibiting sweating and that the reason for the superior efficacy of using distilled water in the anodal reservoir may be due to the marked acidification of the anodal medium. Hence, we tested whether the initial pH of the anodal reservoir influenced the efficacy of the anodal current. As predicted, the acidic medium was found to be superior to the alkaline medium (Fig. 6).

Response of sweat gland after TWI in vivo and in vitro. Because it is likely that the sweat gland (especially the sweat duct) is subjected to a highly acidic environment

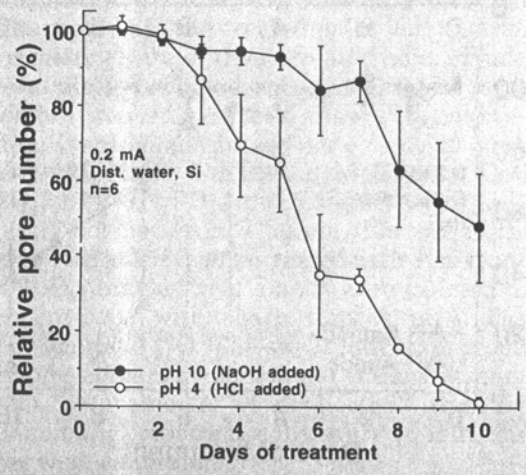

FIG. 6. Effect of pH of initial anodal medium on efficacy of iontophoresis. pH was adjusted by titrating water with 1 N HCl (for pH = 4) or NaOH (pH = 10). Difference between 2 groups was significant ($P < 0.01$) from *day 7* to *day 10*. Test sites for both controls and experimentals were coated with silicone and treated daily at 0.2 mA/cm^2.

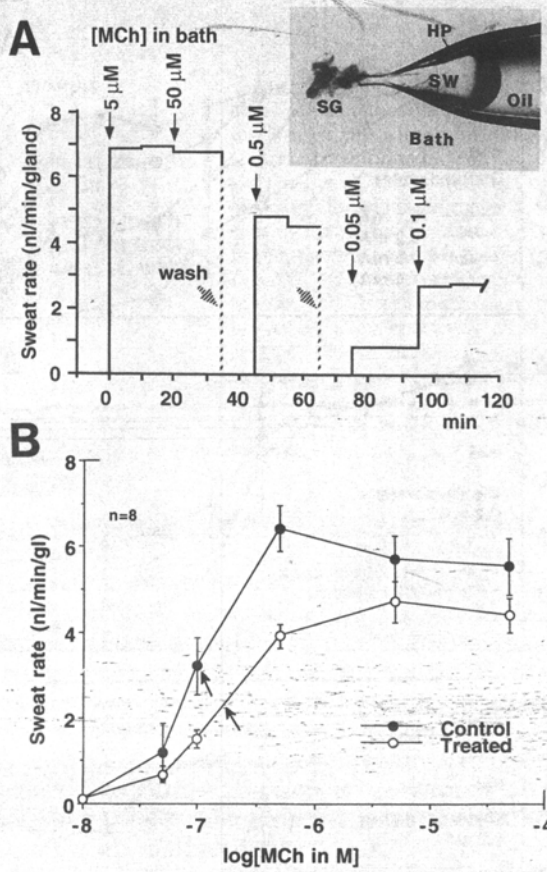

FIG. 7. *A*: example of sweat induction from isolated control sweat gland in vitro. Open end of proximal duct with attached secretory coil (SG in *inset*) was held by suction to oil-filled holding pipette (HP) and sealed with Silgard (Dow Corning, Midland, MI). Sweat (SW) was induced in bicarbonate-buffered Ringer solution kept at 37°C (Bath) by addition of methacholine (MCh). At "wash," incubation medium was changed to prewarmed Ringer solution. Concentrations of MCh ([MCh]) in bath are shown. Sweat samples were collected with oil-filled inner pipette (not shown in *inset*) every 10 min. *B*: dose response of MCh-induced sweating from isolated sweat glands in vitro. Eight sweat glands each for both "control" (untreated) and "treated" were derived from 2 subjects. $P < 0.01$ for 5×10^{-7} and 10^{-7} M MCh and $0.05 < P < 0.07$ for other doses. Arrows, mean effective doses of [MCh] for control and treated (10^{-7} and 1.8×10^{-7} M). Note small rightward shift of curve after treatment.

for 30 min daily for 7–14 days during TWI, we addressed whether the secretory coil would remain intact during the course of TWI. Because finger tips are not the most suitable experimental sites for skin biopsies or the injection of drugs, we used the thenar area of the palm. To induce complete anhidrosis, we treated two subjects with severe palmar hyperhidrosis with conventional TWI, except that Vaseline was used to insulate the epidermis. After 7 days of daily 30-min treatments at 20–25 mA, the completely anhidrotic areas of the palm were localized with iodinated paper (data not shown). We also confirmed that the skin area devoid of active sweat pores failed to show any output of sweat from the skin surface even under the strongest pharmacological stimulus, i.e., intradermal injection of 0.5 mM methacholine (data not shown). We then biopsied an adjacent anhidrotic area, isolated a single sweat gland, and stimulated it in vitro (Fig. 7*A*). All the sweat glands from the control sites responded to varying doses of MCh for >2 h, indicating the

reliability of the in vitro system. The sweat glands isolated from the treated skin specimens tended to show lower sweat rates, i.e., from 18 to 37% lower at MCh concentrations $>5 \times 10^{-7}$ M, and the sweat rate tended to decline with time (data not shown). Furthermore, there was a rightward shift of the effective dose that elicits 50% of the maximal sweat rate in the treated glands compared with the control glands (Fig. 7*B*), suggesting that the pharmacological responsiveness of the glands and the robustness of glandular activity were also lowered after treatment with TWI.

DISCUSSION

The inhibitory effect of anodal galvanic current on eccrine sweating has been exploited for the treatment of excessive sweating on the palms and soles for nearly 50 years (1, 6, 7, 14). Unfortunately, the basic mechanism of sweat inhibition by TWI is still poorly understood. This is partly because palmar sweating is difficult to study because of the emotional nature of the sudomotor drive and the anatomic complexity of palmar skin. Furthermore, the lack of a simple methodology has prevented us from treating the skin and analyzing the data in a controlled quantitative manner. Therefore, our first effort was directed at improving the available methodology for studying the palmar sweat glands. Summarizing the present results, we have confirmed that some of the earlier observations made in studies of the sweat glands on the back or forearm (13, 15) partially apply to the palmar sweat glands; namely, anodal current is superior to cathodal current, water is superior to saline, and current-induced inhibition of sweating is a function of the current density. We then observed that current passing through the pores, rather than the epidermis, is critical for inducing anhidrosis. This is based on the observation that placing a layer of insulating material such as silicone grease (or perhaps Vaseline) on the skin reduced the total skin conductance by 60% without occluding the sweat pores. The silicone coating also prevented the swelling of the stratum corneum in water and the subsequent swelling-induced transient occlusion of the sweat pores. Because the total current density was kept constant at 0.2 mA/cm^2, silicone coating of the skin should have effectively increased the current density at the sweat pores ~2.5-fold. This notion is supported by the observation that treatment at 0.2 mA/cm^2 under silicone coating enhanced the efficacy of iontophoresis to the level that was achieved by 0.5 mA/cm^2 without silicone coating (see Fig. 3).

What is the mechanism whereby the anodal current is controlling sweating? We observed that the pH of the anodal reservoir dropped to ~3, whereas that of the cathodal reservoir increased to ~10 during TWI, most likely due to hydrolysis of water at the steel electrode. It is also noteworthy that when the same experiment was repeated with saline (NaCl dissolved in distilled water, 150 mM) as the anodal solution, the pH of the saline did not drop significantly. Thus, it is the strong acidity generated by hydrolysis of water that may be the major factor in the TWI-induced inhibition of sweating. This also explains why using saline as the anodal solution or using

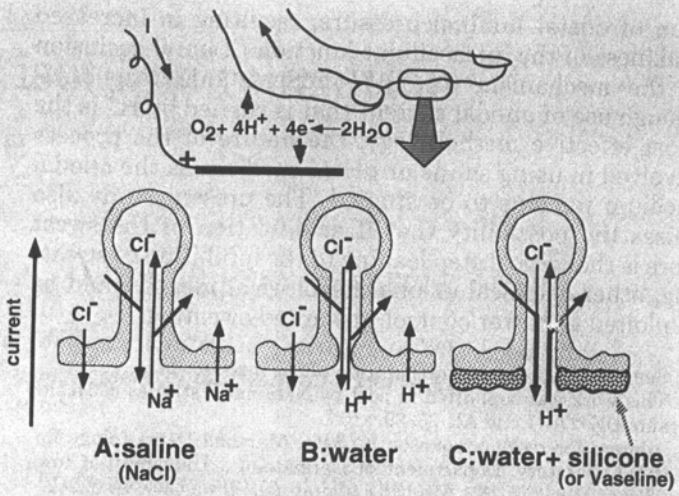

FIG. 8. Schematic diagram showing possible pathways of ionic movement during iontophoresis. *Top*: equation for hydrolysis of water resulting in generation of H^+. *Bottom*: blow-up of skin section indicated by large shaded arrow. *A*: saline is used as anodal solution. *B*: water is used as anodal solution but without silicone coating of skin as in conventional protocol for tap water iontophoresis. *C*: water is used as anodal solution with skin coated with silicone (or any insulating material such as Vaseline). *I*, current.

cathodal current (regardless of the medium used) is less inhibitory because H^+ is not generated. In support of such a thesis, the acidic anodal reservoir solution was much more effective than the alkaline solution (see Fig. 6). In aqueous solutions, the electric current is carried by charged particles or ions. With NaCl in the anodal reservoir (Fig. 8*A*), the current is carried by the forward movement of Na^+ and the backward movement of Cl^-. The reaction $2Cl^- = Cl_2 + 2e^-$ may provide the necessary electrons for the anodal electrode without resorting to the hydrolysis of water. However, with water in the anodal reservoir, the current is carried mainly by the backward movement of Cl^- initially and later, as more H^+ is generated, by the forward movement of H^+ and the backward movement of Cl^-. This causes the sweat pores and the ductal lumen to become even more acidic than the external medium because H^+ accumulates and moves through the narrow sweat pores and the duct, especially when the epidermis is insulated by silicone or Vaseline. Then, what is the consequence of H^+ accumulation in the ductal lumen in relation to TWI-induced inhibition of sweating? As shown in Fig. 7, sweat glands isolated from the (TWI-induced) anhidrotic palmar skin were still able to respond to MCh, although not to the same extent as the control glands. The present study has not addressed the precise sites and nature of injury in the distal segment of the duct and/or the sweat pores because sweat was collected from the end of the proximal duct (for technical reasons). The fact that the sweat glands isolated from completely treated sites showed slightly lower pharmacological responsiveness (as indicated by the rightward shift of the dose-response curve), somewhat decreased robustness of secretory activity in vitro, and a slightly lower sweat rate suggests that the secretory portion is also partially affected by exposure to intense acidity during TWI. Alternatively, it is possible to speculate that the decreased sweat production is a secondary phenomenon; e.g., chronic ductal obstruction caused a persistent eleva-

tion of ductal luminal pressure, resulting in increased leakiness of the intracellular junction (if poral occlusion is the mechanism for TWI-induced anhidrosis). Although use of anodal current that is carried by H^+ is the most effective methodology, the nature of the process involved in using saline or pH 10 medium as the anodal medium remains to be studied. The present study also raises the possibility that if acidification of the sweat pore is the critical step leading to the inhibition of sweating, other chemical or pharmacological means could be exploited to better control unwanted sweating.

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