Sweat secretion by human axillary apoeccrine sweat gland in vitro

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SATO, KENZO, AND FUSAKO SATO. *Sweat secretion by human axillary apoeccrine sweat gland in vitro.* Am. J. Physiol. 252 (Regulatory Integrative Comp. Physiol. 21): R181–R187, 1987.—Functional characteristics of isolated single human axillary apoeccrine sweat glands have been studied using in vitro sweat induction methods. Sustained copious clear fluid secretion was evoked by methacholine (MCh), epinephrine (EP), isoproterenol (ISO), and phenylephrine (PL) in decreasing order in a pharmacologically specific manner. Apoeccrine glands showed a higher cholinergic sensitivity than eccrine sweat glands, as shown by the apparent association constant for MCh of 2.7×10^{-7} M compared with 2.1×10^{-6} M for the axillary eccrine sweat gland. The average total sweat rate of the apoeccrine gland for a 30-min period was sevenfold higher than that of the eccrine sweat gland. In contrast, isolated apocrine glands showed intermittent pulsatile turbid sweat secretion in response to MCh or EP. The Na^+ and K^+ concentration of apoeccrine glands was nearly isotonic, whereas those of apocrine sweat was 120–140 mM for Na^+ and 10–20 mM for K^+. Apoeccrine ductal Na^+ absorption was also observed in the apoeccrine glands and was no more efficient than that of the axillary eccrine sweat gland. Thus apoeccrine sweat glands are functionally and pharmacologically distinct from axillary apocrine glands and significantly contribute to overall axillary sweating in humans.

eccrine; apocrine; sweating; acetylcholine; isoproterenol

IN A PRECEDING COMMUNICATION (10), evidence was presented to indicate that a third type of sweat gland, the "apoeccrine gland," exists in human axillae. It appears to develop during puberty from eccrine sweat glands or eccrinelike precursor glands. Well-developed apoeccrine glands are much larger than eccrine sweat glands (10, also see Fig. 1) and are as numerous as eccrine or apocrine glands in adult axillary skin. The long duct of these glands also suggests that they may perform avid fluid secretion because conservation of electrolytes is generally the principal function of the sweat duct. Thus, in the present communication we attempt to determine whether the apoeccrine gland is capable of copious fluid secretion as in the eccrine sweat gland, and if so, what is its pharmacological basis. The secretory epithelium of both the apoeccrine gland and the classical apocrine gland exhibits a similar anatomical feature, i.e., a single layer of tall columnar secretory cells overriding the layer of myoepithelium. Comparative study of these two apocrine epithelia will thus provide insight into the long-held mystery as to why some apocrine glands (e.g., ceruminous apocrine glands in the external ear canal) perform thick viscous secretion, whereas apocrine glands of some animals are capable of persistent fluid secretion. The latter is instrumental in thermoregulation through evaporative heat loss (2–7).

Similarly, comparative analysis of eccrine and apocrine secretory epithelia relative to secretory rate, electrolyte composition of secretory fluid, and pharmacological basis of sweat secretion will also provide insight into the functional significance of cellular organization in these epithelia. As it turned out, the apoeccrine gland is capable of sustained copious fluid secretion in response to both cholinergic and adrenergic stimulation, indicating that apoeccrine secretion significantly contributes to overall axillary sweating.

MATERIALS AND METHODS

Isolation of sweat gland. Biopsy skin specimens obtained from 17 volunteers (ages 18 yr or older) for the companion study (10) were also used in a parallel fashion for the present physiological study. Briefly, a small elliptical skin specimen, 1 cm long and 0.5 cm wide, was excised from the axillary vault under local block anesthesia with 1% lidocaine, sliced, and placed in several changes of Krebs-Ringer bicarbonate solution (KRB) containing the following (in mM): 115 NaCl, 10 sodium acetate, 5 KCl, 1.2 $MgCl_2$, 25 $NaHCO_3$, 1.2 NaH_2PO_4, 5.5 glucose, and 10 mg/100 ml human serum albumin (Sigma, St. Louis, MO) constantly equilibrated with 5% CO_2-95% O_2 (pH 7.45) at 10°C. In a typical experiment, 10–20 sweat glands not used for light- and electron-microscopic studies, or those glands isolated from the other half of biopsy specimens, were placed on the bottom of an isolation chamber. Those glands meeting the criteria of the typical eccrine, apoeccrine, and classical apocrine were selected for sweat induction study. Although morphology of a typical eccrine (Fig. 1*A*) or apocrine gland (Fig. 1*D*) is straightforward, a wide variation of gross morphology was noted in the apoeccrine sweat gland (10).[1] Since the nature of the nondilated

[1] Defined briefly, the apoeccrine glands represent those human axillary sweat glands found in puberty and adulthood that are neither typically apocrine nor eccrine but are in different stages of apocrine differentiation from the eccrine or eccrinelike sweat glands. Thus a number of criteria listed in Table 2 in Ref. 10 must be examined to distinguish them from the classical eccrine and apocrine glands.

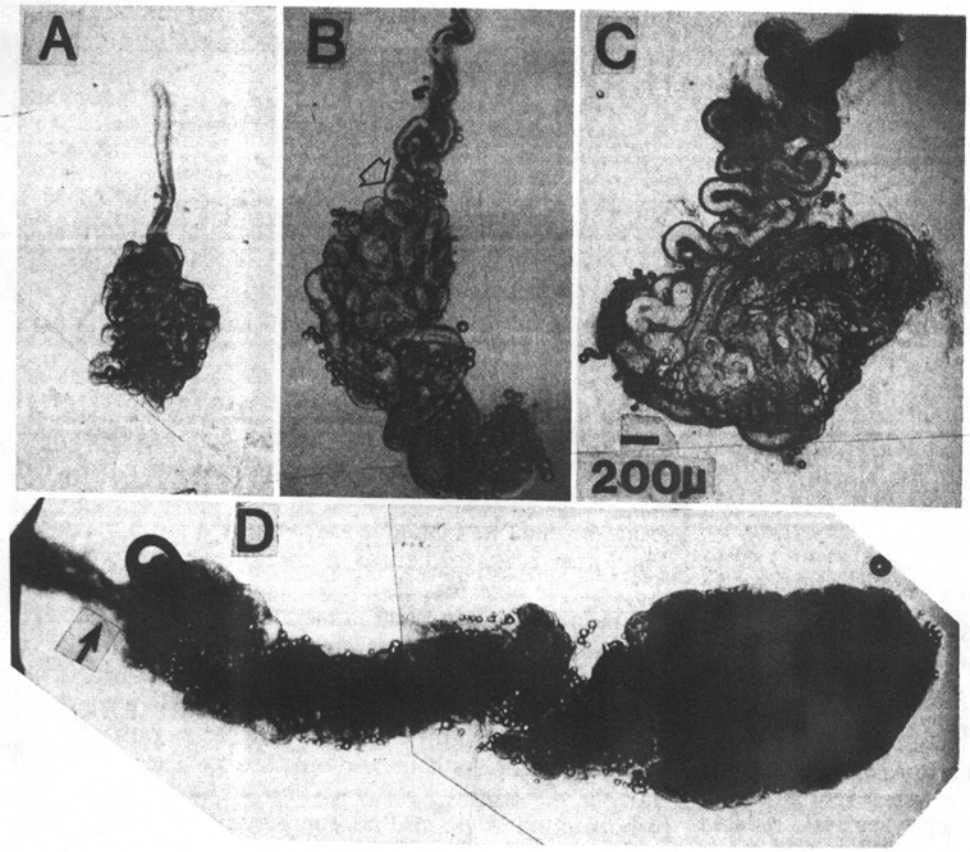

FIG. 1. Typical apoeccrine glands selected for sweat induction study showing varying degrees of differentiation (*B* and *C*). Apoeccrine gland in *B* is nearly completely developed over at least 80% of its secretory coil segment, whereas gland in *C* is fully matured (dilated). A typical eccrine gland (*A*) and a typical isolated single apocrine gland (*D*) are also shown for sake of comparison. *Arrow* in *D* indicates a short, thick apocrine duct. All 4 glands shown are derived from same subject. Magnifications are same for all glands.

tubular segment of the apoeccrine gland is not well defined, we selected only those glands whose tubules were dilated (at least more than twice the diameter of the eccrine secretory coil) over 80% or more of the entire tubular length. Figure 1 shows an illustrative example of the apoeccrine glands selected for sweat induction study, the gland shown in Fig. 1*B* meets the minimal requirements for selection, and the gland shown in Fig. 1*C* is fully developed (obtained from the same individual). In the present study, no attempt was made to correlate the degree of maturity (i.e., the extent of tubular dilation) and function.

For the pharmacological study and the study of electrolyte composition of ductal sweat, the whole apoeccrine sweat gland was used. The apoeccrine gland usually shows varying lengths of the coiled (proximal) portion of the duct (Fig. 2) and the distal straight duct. However, since the straight duct tended to be damaged during dissection, only a short segment (usually 500–700 μm) of the distal duct was left with the sweat gland. Sweat samples were collected from the open end of the distal duct held in a constriction pipette. Thus, the approximate length of the mainly proximal ductal segment attached to the gland varied from 3.5 to 5.5 mm, which is comparable to that of the eccrine sweat gland, which ranged from 3.0 to 4.5 mm. When sweat was collected directly from the secretory coil (to analyze electrolyte composition of secretory fluid), the dilated segment of the secretory tubule was carefully uncoiled and cut for subsequent cannulation. Thus no attempt was made to measure the size of the secretory portion studied, although ~50–80% of the entire secretory coil segment was used for such a study. A limited attempt was made to isolate apocrine glands by dissecting out its short duct from the hair follicle (Fig. 1*D*).

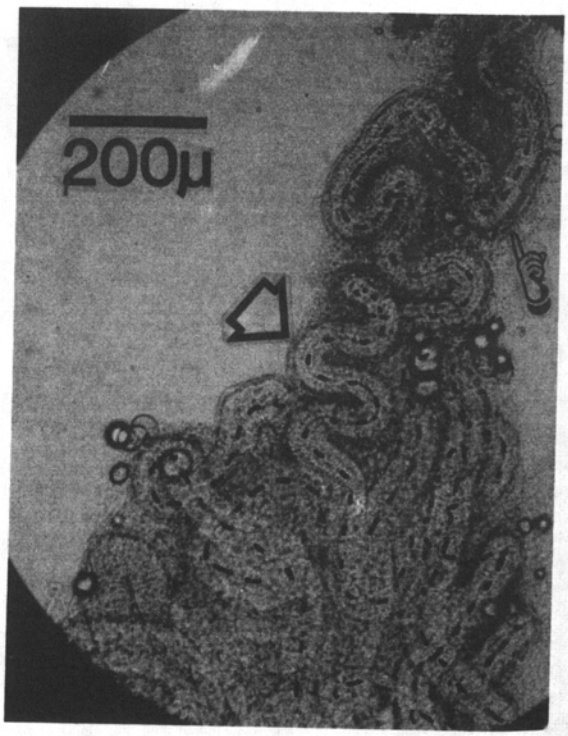

FIG. 2. Coiled proximal duct of an apoeccrine sweat gland whose lumen is outlined with a *dotted line*. This is a higher magnification of same gland shown in Fig. 1*B*. *Open arrow* in Figs. 1*B* and 2 indicates same ductal segment. *Finger* points to approximate area of junction between proximal (coiled) duct and distal duct.

Sweat induction in vitro. Methods of sweat induction

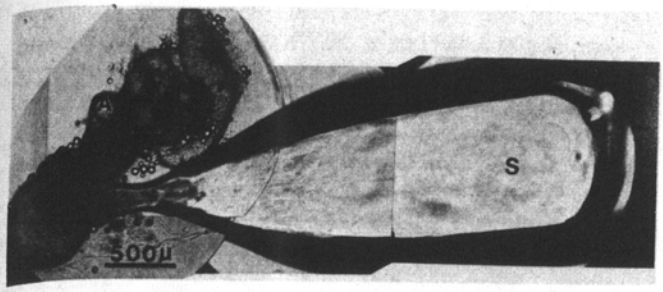

FIG. 3. Sweat induction from an isolated secretory segment of an apoeccrine sweat gland. A, dilated segment of secretory tubule; S, sweat droplet in oil-filled constriction pipette.

from an isolated sweat gland have been previously described (9, 13). Briefly, the cut end of the secretory coil segment or the duct was gently suctioned into a constriction pipette in KRB at 10°C. The tissue-glass junction was effectively sealed with Sylgard 184 (Dow Corning, Midland, MI). The temperature of the bath was slowly increased to 37°C. Spontaneous sweat secretion occurred in some apocrine and apoeccrine glands upon warming the bath, but it was usually only transient. When methacholine (MCh) was added to the incubation bath, a droplet of sweat was seen to enter the oil-filled constriction pipette (Fig. 3) and was collected therein usually every 5 or 10 min. The volumes of the sweat samples were calibrated with a constant-bore calibration pipette. Na^+ and K^+ concentrations in sweat samples were determined with a helium glow spectrophotometer (Aminco Bowman, Silver Spring, MD) using standard solutions containing electrolyte concentrations comparable to the sweat samples.

Micropuncture of apocrine glands. In five apocrine glands, sweat samples were obtained directly from the dilated secretory coil lumen by use of the micropuncture technique (10, 17) during stimulation with 5×10^{-6} M MCh at 37°C. This was done because isolating the apocrine gland for sweat induction study was rather tedious and was likely to result in damage to the gland. Rather, the apocrine gland did not have to be completely freed of surrounding connective tissue or the epidermis to prepare for micropuncture study. The puncture site was gently immobilized by a glass hook and a glass ring. The micropuncture pipette was previously filled with mineral oil colored with Sudan black III and ~30–50 nl of sweat were easily obtained from each puncture by gentle suction. These samples were immediately subjected to the helium glow spectrophotometer for determining Na^+ and K^+ concentrations. Unless otherwise specified, all the reagents were obtained from Sigma (St. Louis, MO).

RESULTS

Pharmacological responsiveness of apoeccrine glands. As shown in Fig. 4, immediately upon stimulation of apoeccrine glands with MCh, sustained copious fluid secretion was evoked. Secreted fluid was visually as serous (i.e., not turbid) as eccrine sweat, in contrast to typical apocrine sweat, which is cloudy when seen under a stereomicroscope. MCh-evoked sweat secretion was completely inhibited by atropine (AT) (Fig. 4). Like

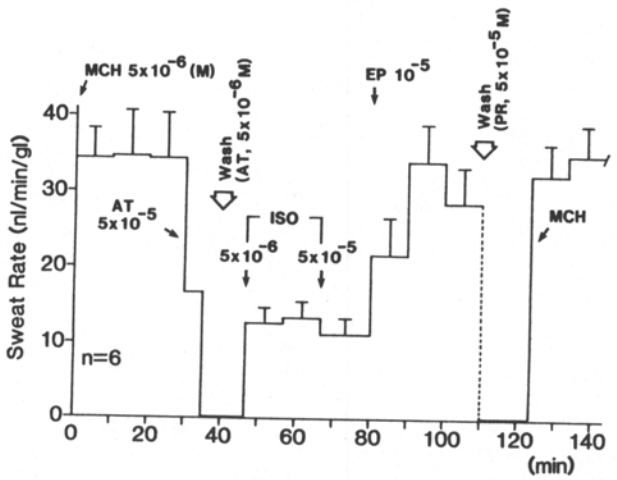

FIG. 4. Sweat secretion by isolated apoeccrine sweat glands in vitro. At *time 0*, 5×10^{-6} M methacholine (MCh) was added to bath. After inhibition of MCh sweating by 5×10^{-5} M atropine (AT), isoproterenol (ISO) and epinephrine (EP) had been added to bath as indicated by *open arrows*, incubation bath was replaced several times with fresh Krebs-Ringer bicarbonate containing 5×10^{-6} M AT. PR, propranolol.

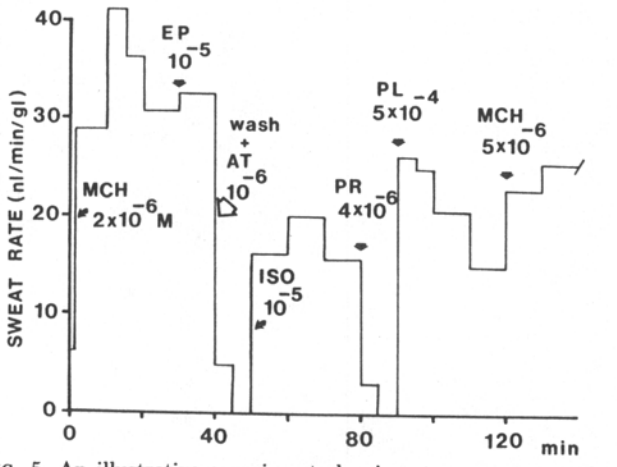

FIG. 5. An illustrative experiment showing strong response of an apoeccrine gland to phenylephrine (PL). Also note inhibition of isoproterenol (ISO) sweating by propranolol (PR). Epinephrine (EP) stimulation superimposed on maximal methacholine (MCh) stimulation showed negligible enhancement of sweat rate.

normal eccrine sweat glands, the apoeccrine glands also responded to isoproterenol (ISO) and to epinephrine (EP). EP yielded a sweat rate comparable to or only slightly lower than the maximal MCh sweat rate. This strong responsiveness to EP may be due to its combined α and β effect because in some apoeccrine glands a high concentration of phenylephrine (PL, 5×10^{-4} M) alone evoked transient but strong secretory response (Fig. 5). Specificity of ISO-induced sweating is also shown by its inhibition by propranolol (PR) (Fig. 5). Figures 6 and 7 summarize the relative sweat rate of apoeccrine glands due to ISO and EP,[2] respectively, which is significantly higher than that of eccrine sweat glands on the forearm and the back (11). Of the four axillary eccrine sweat glands depicted in Fig. 6, ISO responsiveness of three glands were comparable to that of forearm and back

[2] Relative ISO (or EP) sweat $rate_{max}$ is defined as the maximal ISO (or EP)-induced sweat rate divided by the maximal cholinergic (MCh) sweat rate in the same sweat gland.

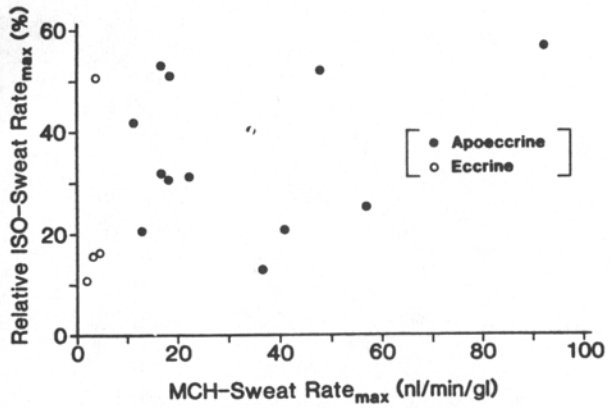

FIG. 6. Relative isoproterenol (ISO) responsiveness of axillary apoeccrine and eccrine sweat glands. *Each plot* represents a single sweat gland where maximal sweat rate to both methacholine (MCh, 5×10^{-6} M) and ISO (5×10^{-5} M) was determined as in experiment in Fig. 4. During stimulation with ISO, about half of experiments did not use phentolamine (an α-adrenergic antagonist, 10^{-5} M). However, since no systematic difference was noted relative to ISO responsiveness with or without phentolamine, data were depicted altogether. Complete inhibition of ISO sweating by PR (see also Fig. 4) also supports negligible endogenous (periglandular) adrenergic stimulation.

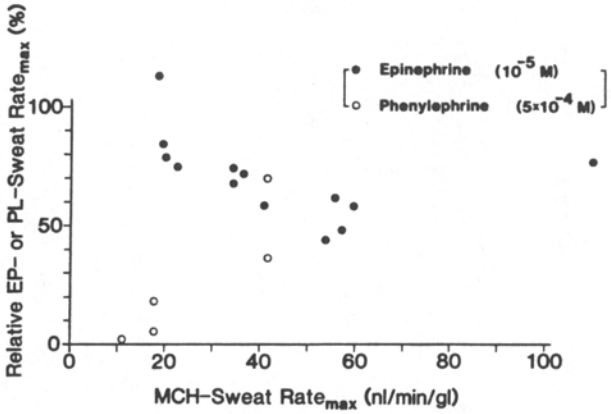

FIG. 7. Relative epinephrine (EP) or phenylephrine (PL) responsiveness of apoeccrine sweat glands. Propranolol was always added to medium during stimulation with PL. Likewise, atropine was always present during adrenergic stimulation (i.e., EP, isoproterenol, PL).

eccrine glands, although one axillary eccrine gland avidly responded to ISO (i.e., the relative ISO sweat rate of 51%). Figure 6 also shows that maximal MCh sweat rates of apoeccrine glands are many fold higher than those of eccrine sweat glands isolated from the axillae. Figure 7 also shows that α-adrenergic (i.e., PL) responsiveness of apoeccrine glands varies widely among different glands despite the fact that relative EP responsiveness is consistent. This indicates that a more consistent secretory response is achieved with a combination of α and β stimulation (as after stimulation with EP) than with either one component of adrenergic stimulation. In fact, as shown in Fig. 8, K_a (apparent association constant for agonists) for EP (see Ref. 13 for method of calculation) is more than one order of magnitude smaller than for ISO, indicating higher pharmacological sensitivity of apoeccrine glands to EP than to ISO. Nevertheless, it must be noted that MCh is the strongest agonist for sweat secretion by apoeccrine sweat glands (Figs. 6 and 7). When a comparison of MCh sensitivity was made between the apoeccrine and axillary eccrine sweat gland, K_a for the apoeccrine gland was about one order of magnitude smaller than that for the eccrine sweat gland, indicating that sensitivity of apoeccrine glands to MCh is higher than that of the eccrine glands (Fig. 9). Classical apocrine glands were also cannulated and stimulated. Upon stimulation with either MCh or EP there was a transient output of very turbid secretory fluid that lasted

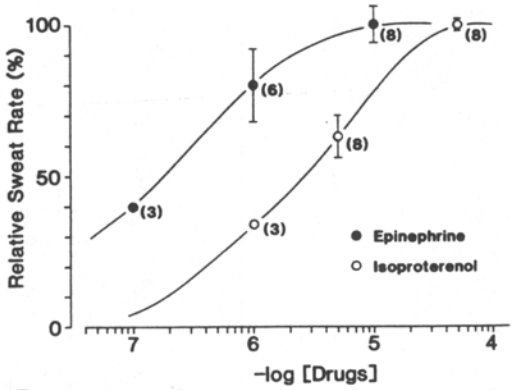

FIG. 8. Dose response of apoeccrine sweat rate to epinephrine and isoproterenol. In each gland sweat rate was expressed relative to maximal sweat rate (which is 100%). Number of glands studied is given in parentheses. *Each plot* is mean ± SE.

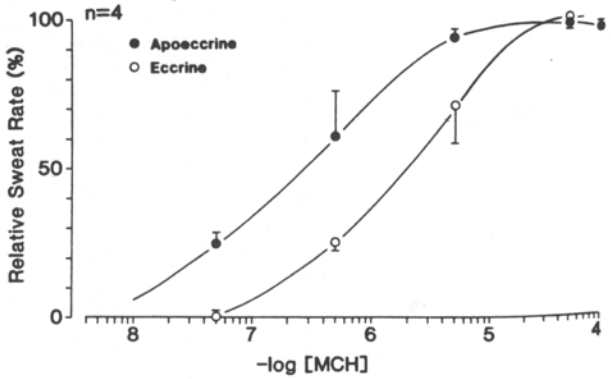

FIG. 9. Comparison of dose response to methacholine (MCh) of relative sweat rate between axillary apoeccrine and eccrine sweat glands. Apparent association constant for MCh was 2.7×10^{-7} M for apoeccrine glands and 2.1×10^{-6} M for eccrine glands.

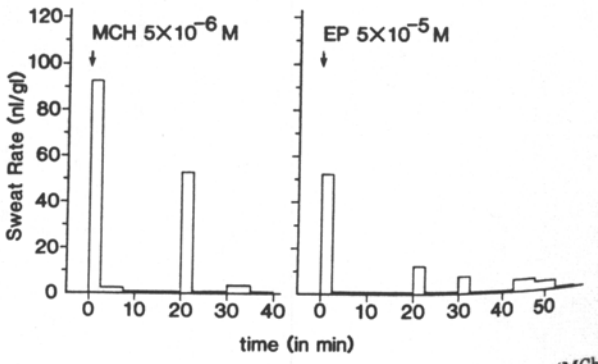

FIG. 10. Intermittent sweating responses to methacholine (MCh) and epinephrine (EP) in 2 apocrine glands. Second or third pulsatile sweat secretion occurred spontaneously while initially added drugs were continuously present in bath.

for <3 min. At this point, higher doses of MCh or EP or a combination of the two were added to the bath, but without any secretory response. In six apocrine glands, secretion never resumed in 30 min and the experiment was discontinued. However, in two apocrine glands, a second or third transient secretory response occurred at 20 and 30 min of incubation without further pharmacological manipulation (Fig. 10). Overall, MCh appeared to be a slightly stronger stimulant of apocrine sweat secretion than EP; however, since different glands were used, no statistical analysis can be made. To quantitatively estimate which type of sweat gland principally contributes to sustained axillary sweating, we plotted the total sweat rate per gland over the initial 30-min period of sweat induction.

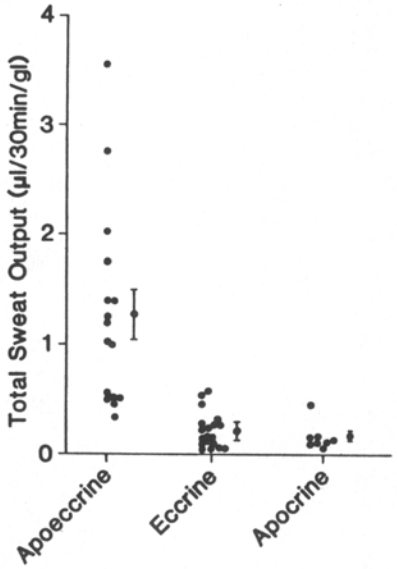

FIG. 11. Comparison of total sweat output per gland over a 30-min period by 3 types of glands.

As can be seen in Fig. 11, apoeccrine glands elaborate significantly higher sweat rate in vitro on the per gland basis and perhaps also on the per unit area in vivo, since population density of each type of gland is from 50 to 200% that of the eccrine sweat gland.

Electrolyte composition of secretory (primary) fluid induced in vitro. The Na^+ and K^+ concentration of sweat samples collected directly from the isolated segment of apoeccrine secretory tubule is shown in Fig. 12. Since the incubation bath contained 145 mM Na^+ and 5 mM K^+, apoeccrine sweat was approximately isotonic with respect to the sum of Na^+ plus K^+ concentrations. Thus slightly hypotonic Na^+ in the low sweat rate range of 142 mM is balanced by slightly hypertonic K^+ concentration of 8.0 mM. At a higher sweat rate range, the average Na^+ concentration rose to 145 mM, but K^+ concentration remained at ~8–9 mM. Figure 12 also shows Na^+ and K^+ concentrations in the five apocrine sweat samples obtained by the micropuncture technique. (Apocrine sweat samples from sweat induction studies were lost during storage before titration of Na^+ and K^+ concentration.) Interestingly, the apocrine secretory fluid contained hypotonic Na^+ (from 120 to 140 mM) concentration, whereas K^+ concentration ranged from 10 to 20 mM. Because of the transient and periodical nature of apocrine secretion (see Fig. 10) and because the apocrine gland is always filled with abundant preformed sweat, the micropuncture samples may be the mixture of freshly formed and preformed secretory fluid.

Electrolyte composition of ductal sweat samples induced in vitro. As shown in Fig. 13, Na^+ concentration of apoeccrine sweat samples collected from the early segment of the distal (straight) duct was variably hypotonic to the bath at the low sweat rate range indicating ductal Na^+ absorption. However, at the mid to high sweat rate range it approached isotonicity. This could be partially due to saturation of the ductal capacity for Na^+ absorption because of an excessively high sweat rate, despite

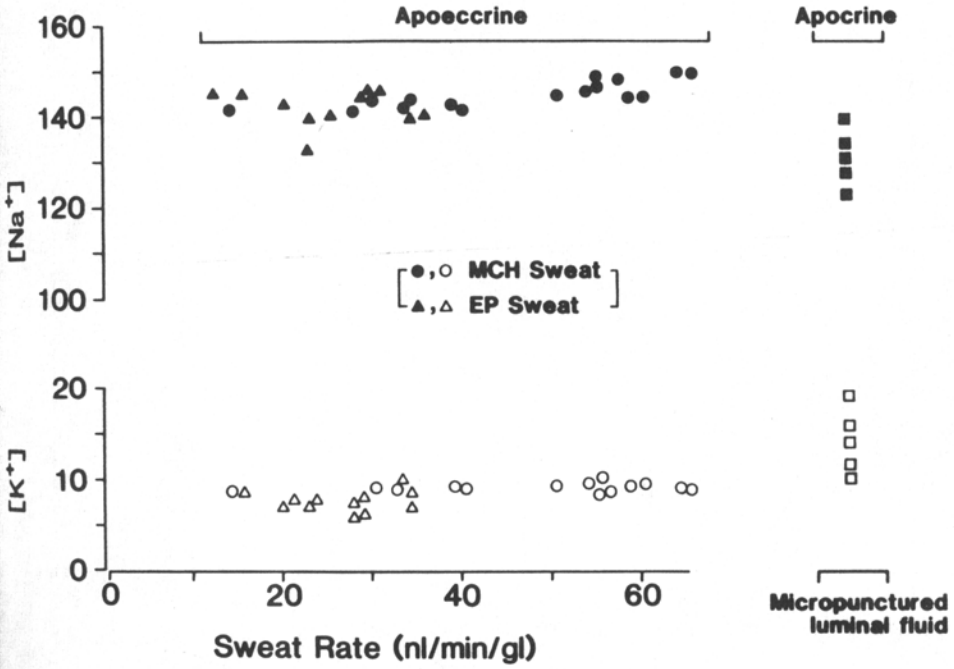

FIG. 12. Na^+ and K^+ concentrations of apoeccrine and apocrine secretory (primary) fluid. *Solid symbols*, Na^+ concentration; *open symbols*, K^+ concentration. Apoeccrine samples were obtained by sweat induction from 6 isolated apoeccrine secretory tubules, whereas apocrine samples were obtained from 5 apocrine glands by micropuncture technique. In Figs. 12–14, different sweat rates were obtained in each sweat gland by increasing dose of agonists. Note that incubation bath (Krebs-Ringer bicarbonate) contained 151.2 mM Na^+ and 5 mM K^+. MCh, methacholine; EP, epinephrine.

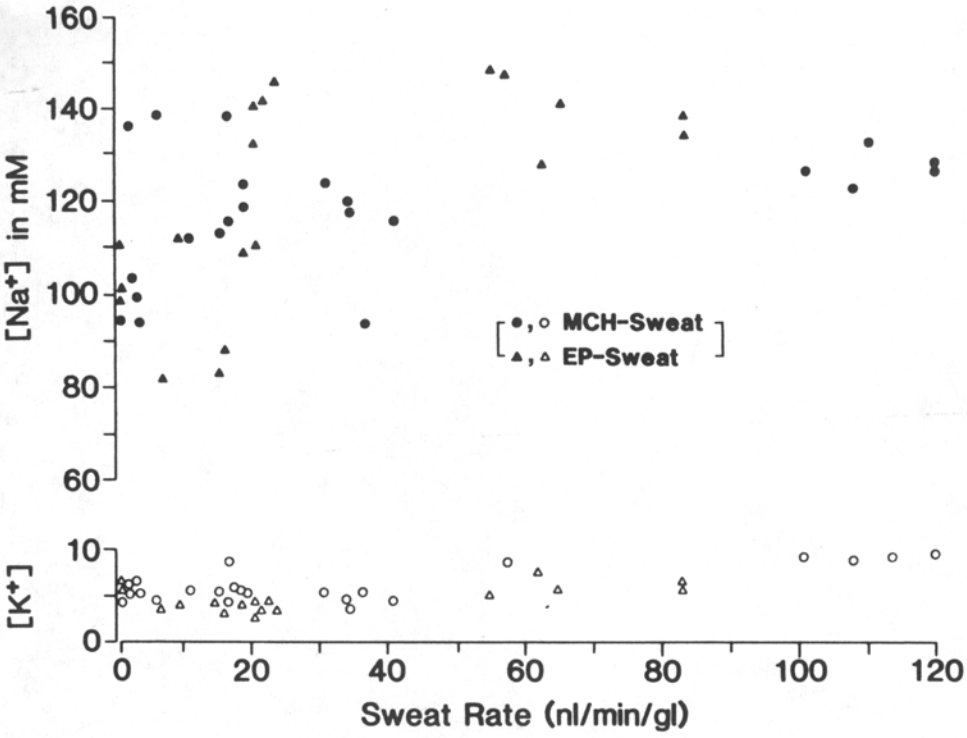

FIG. 13. Na^+ and K^+ concentrations of apoeccrine ductal sweat induced in vitro. Sweat samples were collected from end of early distal segment of apoeccrine duct. *Plots* represent sweat samples from 10 apoeccrine glands. MCh, methacholine; EP, epinephrine.

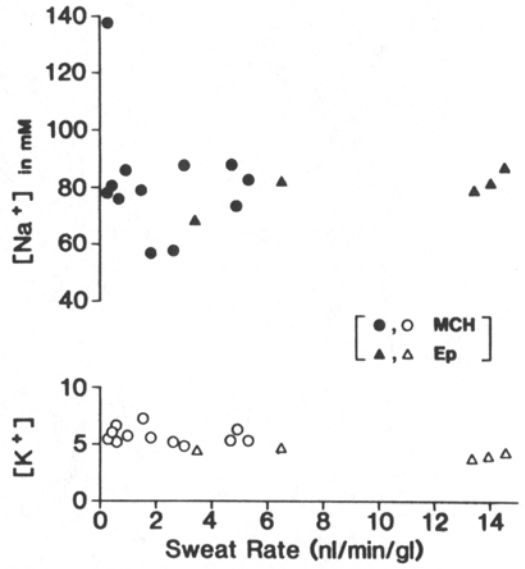

FIG. 14. Na^+ and K^+ concentrations of axillary eccrine sweat. Sweat samples were collected from early segment of distal duct. Data are derived from 4 sweat glands. MCh, methacholine; EP, epinephrine.

the fact that the length of the apoeccrine sweat duct is comparable to that of the eccrine sweat duct (see Fig. 2). Nevertheless, even the lowest Na^+ concentration at the very low sweat rate range did not dip below 80 mM, suggesting that the apoeccrine duct is no more efficient in reabsorbing Na^+ than the axillary eccrine sweat duct (Fig. 14) (mean ± SE of Na^+ concentration for the sweat rate of between 0 and 10 $nl \cdot min^{-1} \cdot gland^{-1}$ is 104.7 ± 6.1 for the apoeccrine gland and 81.2 ± 5.8 for the eccrine sweat gland ($P < 0.05$)).

DISCUSSION

The term apoeccrine sweat gland has been conveniently coined to designate those sweat glands abundantly present in human adult axillae which are morphologically distinct from typical eccrine and apocrine sweat glands (10, also see Fig. 1). The purpose of this study was therefore to elucidate whether the apoeccrine gland also shows functional characteristics distinct from the two other types of sweat glands. We have observed that the apoeccrine gland is capable of very avid sustained fluid secretion in response to MCh, EP, and ISO (in a decreasing order) in a pharmacologically specific manner. Its secretory (primary) fluid is nearly isotonic to the bathing medium with respect to Na^+ concentration, although K^+ concentration is slightly higher than that of the bathing medium (5 mM). Thus its pharmacology and secretory activity are very comparable to those of the eccrine sweat gland. Not only is the apoeccrine gland many times larger than the adjacent eccrine sweat gland, and thus its secretory rate also many times larger than that of the eccrine sweat gland, but the apoeccrine gland has one more important functional characteristic: it demonstrates a higher sensitivity (and thus a smaller K_a value) to MCh stimulation. This is in keeping with the thesis proposed for the (nonaxillary) eccrine sweat gland that the increased MCh sensitivity is one of the important characteristics of functionally active eccrine sweat glands (12). If it is assumed that apoeccrine and eccrine glands occur in about the same number in the adult axillae (actually the ratio of the two types of glands varies from 50 to 200% as shown in Ref. 10), apoeccrine glands are capable of turning out a sevenfold larger volume of axillary sweat than the eccrine sweat gland at the supramaximal MCh concentrations (see Fig. 11).

To the best of our knowledge, this study is the first attempt at inducing apocrine secretion from isolated human axillary glands in vitro. Consistent with the long-held notion that apocrine sweat is thick and milky (15), we also observed viscous and cloudy apocrine secretion that occurred only briefly in response to MCh as well as EP stimulation. In two glands, such transient secretion resumed after a latent period of 20 min (see Fig. 10). It could be argued that such an intermittent pulsatile secretion could be due to myoepithelial contraction. However, this may not be the case because MCh stimulation, which does not cause myoepithelial contraction (8), induced sweat secretion comparable to EP, which induces myoepithelial contraction (8). Responsiveness of axillary apocrine glands to both adrenergic and cholinergic agents in vivo has been observed by Aoki (1). The high K^+ (10–20 mM) and the hypotonic Na^+ (120–140 mM) concentration in the apocrine secretory fluid is also noteworthy, especially because the sweat samples obtained by the micropuncture technique may partially constitute the preformed luminal fluid.

A question arises as to why the apparently similar single layer of columnar epithelium is capable of sustained copious serous fluid secretion as in the apoeccrine gland on the one hand and a thick, viscous scanty secretion as in the apocrine gland on the other. In this respect, the apocrinelike secretory epithelium of human axillary apoeccrine gland is functionally more akin to that of epitrichial apocrine glands in some animals (2–7) and that of eccrine secretory coils which are capable of sustained fluid secretion. As has been repeatedly shown, functional heterogeneity exists in different apocrine glands in humans and other animals and the term apocrine cannot be restricted to those glands that mainly perform thick viscous secretion, presumably through decapitationlike mechanisms. Since the apocrinelike epithelium of the axillary apoeccrine gland performs a secretory function very analogous to the eccrine sweat gland, the study of apoeccrine glands will further our understanding of the secretory mechanism of eccrine sweat glands. In fact, the apoeccrine epithelium may be a far superior investigative model system of exocrine fluid secretion because of a simpler structure, large size and a single cell type. In other words, it could be inferred that the complex structure of eccrine secretory epithelium (e.g., the presence of dark cells, intercellular canaliculi and the intricate basal membrane infoldings) may not be a prerequisite for sweat formation. Equally interesting, its α- and β-adrenergic responsiveness is even higher than that of human eccrine sweat glands. This feature could be exploited to reexamine our recent postulate that the eccrine sweat gland of cystic fibrosis is defective in β-adrenergic responsiveness despite the seemingly normal tissue adenosine 3′,5′-cyclic monophosphate accumulation (11).

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