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THE RESPONSE OF THE SWEAT GLANDS TO SOME LOCALLY ACTING AGENTS IN HUMAN SUBJECTS*

HENRY D. JANOWITZ, M.D., M.S.† AND M. I. GROSSMAN, PH.D., M.D.

In the course of other studies on the autonomic pharmacology of the skin (1, 2, 3) we have had occasion to observe the respones of the human sweat glands to certain locally acting agents.

The observations to be reported are of three main varieties:

(a) Although the responsiveness of the human sweat glands to pilocarpine and acetylcholine (ACh) is well known, there is incomplete information regarding the responses to the *local* application of parasympathomimetic drugs, especially those which act by inhibiting cholinesterase.

(b) The paradoxical failure of denervated sweat glands to respond to the local intracutaneous injection of ACh, first described by Coon and Rothman (18), has been studied by us with a variety of drugs. The responses of these denervated glands to local heat was also observed.

(c) The sex difference in responsiveness of the sweat glands to locally injected ACh was investigated by attempting to determine threshold doses of this drug in a small series of male and female subjects.

(d) We have also made observations on the optimal concentration of ACh for the production of the axon reflex type of sweating response first described by Rothman and Coon (4).

METHODS

The agents employed were either injected in saline solution intracutaneously with a 27 gauge needle, or else, in the case of hexadienol, applied by inunction. Sweating was detected either by the ferric chloride-tannic acid method of Silverman and Powell (5), or by the starch paper and iodine method of Randall (6). The sweating response was graded roughly on a scale of 0 to ++++, where ++++ represented the average response at the end of 1 minute to 0.1 cc. of ACh (1:1000) injected intracutaneously on the forearm of a male subject.

RESULTS

A. *Local responses to intracutaneous injection of parasympathomimetic agents.* In a series of 10 male subjects, 0.1 cc. of the substances listed in Table 1 were injected intracutaneously in the skin of the forearm. An equal volume of physiological saline solution was used as a control, being injected in the contralateral arm. Neither saline nor the trauma of intracutaneous injection was ever observed to produce any local sweating. The results appear in Table 1.

Prostigmine and physostigmine induce local sweating when acting alone and increase the response to ACh.

B. *Responses of post-ganglionically denervated sweat glands.* The responses of

* Department of Clinical Science, University of Illinois, College of Medicine, Chicago, Illinois.

† Welt Fellow in Medicine, Mt. Sinai Hospital, New York City.

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sympathectomized sweat glands to intracutaneously injected parasympathomimetic drugs were studied in 9 patients.

The local sweating induced by the intracutaneous injection of 0.1 cc. of pilocarpine (1:1000), ACh (1:10 to 1:1000), physostigmine (1:1000), prostigmine (1:2000) and ACh plus physostigmine or prostigmine was noted to disappear from the postganglionically denervated area in 4 patients following unilateral lumbar sympathectomy for peripheral vascular disease at 30, 38, 48 hours and 7 days respectively following operation. These patients were followed daily from the day of operation. The unoperated side served as a control, sweating always being elicited there. Five other patients studied for the first time at various intervals after operation were found to have no local sweating response to these drugs in the denervated area at periods of from 3 days to 7 months following operation.

In 10 other patients, hexadienol,[1] which causes localized sweating when applied to the skin by inunction, was tested. This material, a diene-alcohol, has been

TABLE 1

Local response to intracutaneously injected parasympathomimetic drugs in human subjects

DRUG	RESPONSE
ACh (1:1000)	+++
Pilocarpine (1:1000)	+++
Physostigmine (1:1000)	+ to ++
Prostigmine (1:2000)	+ to ++
Carbaminoylcholine (1:2500)	+ to ++
ACh (1:1000) + Prostigmine (1:2000)	++++
ACh (1:1000) + Physostigmine (1:2000)	++++

shown to have a muscarinic effect on sweat glands (7). In two patients with unilateral lumbar sympathectomy for peripheral vascular disease the local sweating induced by hexadienol disappeared in the denervated areas in 30 and 40 hours respectively following operation. Eight hypertensive patients with bilateral thoracolumbar sympathectomy for essential hypertension were tested for the first time at various intervals following operation and were found to have no response to hexadienol applied locally to the denervated area 3 to 18 months after operation. Figure 1 shows the line of demarcation between the innervated and denervated skin as demonstrated by this technic.

Responses of denervated sweat glands to heat. In 2 male patients with unilateral lumbar sympathectomy for peripheral vascular disease in whom the local injection of 0.1 cc. ACh (1:10) failed to cause local sweating after sympathectomy the effect of local heat was studied.

Exposure of the skin to radiant heat (100 watt electric bulb approximately 5 cm. from the skin for 5 minutes) caused definite local sweating to occur. This amount of heat also caused local erythema and blistering.

Attempts to potentiate the action of ACh on denervated skin. In view of the

[1] Obtained through the courtesy of Dr. Theodore Koppanyi, Georgetown University, School of Medicine, Washington, D. C.

evidence that epinephrine may potentiate the action of ACh under certain circumstances (8), an attempt was made to stimulate the denervated sweat glands with mixtures of ACh and epinephrine. In 3 patients in whom ACh failed to stimulate denervated sweat glands, 0.1 cc. of ACh (1:1000) with epinephrine (1:1000, 1:10,000, 1:100,000) likewise failed.

Since it has been suggested (9) that the failure of denervated sweat glands to respond to local injection of ACh may be due to alteration in permeability

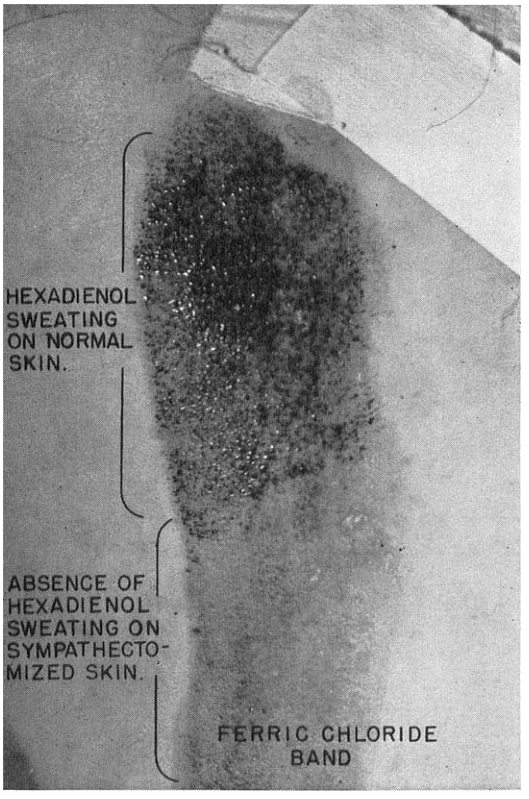

FIG. 1. Boundary between denervated and innervated skin areas is clearly demonstrated with hexadienol induced sweating, three days following dorsolumbar sympathectomy. The occurrence of sweating is detected by the ferric chloride—tannic acid method of Silverman and Powell.

of the glands following denervation, we attempted to facilitate diffusion of ACh by combining it with histamine on the assumption that this substance might alter permeability.

In 4 patients with sympathectomy, addition of histamine (1:1000) to ACh (1:1000) did not induce sweating.

C. *Threshold dosage of ACh for sweat response in males and females.* In view of the difference between men and women in responsiveness of the sweat glands to locally injected ACh, we have attempted to measure roughly the threshold dosage for sweating induced by local injection of ACh in a small series of normal

subjects. In addition the induction of the axon reflex type of sweating which occurs for a considerable distance from the site of injection and which is dependent on the integrity of the postganglionic sympathetic fibers, was observed.

From the results presented in Table 2, it is clear that the threshold for both local and axon reflex sweating induced by intracutaneously injected ACh is higher in the female than in the male. It is equally clear that the threshold for the axon reflex effect is higher than the threshold for local sweat response in both males and females.

TABLE 2

Local and axon reflex type of sweat response to intracutaneously injected ACh in males and females

SUBJECT	SEX	AGE	DOSE OF ACh													
			1:10		1:500		1:1,000		1:25,000		1:50,000		1:100,000		1:1,000,000	
			L	A	L	A	L	A	L	A	L	A	L	A	L	A
C. C.	F	52	++	+	+	+	0	0	0	0	0	0	0	0	0	0
H. B.	F	39	+++	++	++	++	+	+	0	0	0	0	0	0	0	0
S. R.	F	50	+++	+++	++	++	+	+	0	0	0	0	0	0	0	0
F. W.	F	23	++	++	+	+	0	0	0	0	0	0	0	0	0	0
K. F.	F	35	++	++	+	+	0	0	0	0	0	0	0	0	0	0
D. B.	M	29	++++	+++	+++	+++	+++	++	++	+	+	0	+	0	0	0
G. E. R.	M	24	+++	++	+++	++	+++	+	++	+	+	0	+	0	+	0
M. K.	M	35	++++	++	++++	++	+++	+	++	+	++	0	+	0	+	0
C. M.	M	24	+++	++	+++	++	+++	+	++	+	+	+	+	0	+	0
F. A.	M	30	+++	++	++	+	++	+	+	0	+	0	+	0	+	0

L = Local sweating response.
A = Axon sweating response.

DISCUSSION

The observations recorded above indicate that prostigmine and physostigmine which are believed to act by inhibition of cholinesterase are capable of inducing local sweating when injected alone intracutaneously as well as being able to potentiate the action of ACh. The latter observation was well described by Wilson (10). His failure to note the sweating induced by physostigmine alone may be due in part to the method of observing sweating which he employed which was simple observation with a hand lens.

Perhaps the most important conclusion to be drawn from the fact that prostigmine and physostigmine alone induce sweating is that this indicates that ACh is constantly being produced in subthreshold amounts and that the anticholinesterases permit it to built up above threshold levels.

The paradoxical failure of denervated sweat glands to respond to the usual neurohumoral effector, first described by Rothman and co-workers, is not in keeping with Cannon's law of denervation (11) and has not been satisfactorily explained. Rothman (9) has summarized the evidence that this is not due to a degeneration of the sweat gland itself. Kuno (12) has observed a direct response of denervated sweat glands in the foot pad of the cat to excessive local heat. Randall (19) in a study of the effect of radiant heat on sweat glands has noted that procaine and atropine diminished but do not abolish the local response to heating. He did not report on the effect of denervation on this heat induced local

sweating. The present observations are, to our knowledge, the first on the ability of human sweat glands to respond to locally applied heat following their loss of the response to locally injected ACh as a result of denervation. Gurney and Bunnell (13) demonstrated the ability of a sympathectomized limb to respond to local heat; however, this was at a time when the local response to mecholyl was still present.

The failure of epinephrine combined with ACh to stimulate denervated glands is of interest in connection with the potentiating effect of epinephrine on ACh which occurs under certain circumstances, and especially in the light of recent evidence from this laboratory (14) that epinephrine locally elicits sweating in most individuals.

The decreased responsiveness of denervated sweat glands to parasympathomimetic agents is not the first instance of non-conformity with Cannon's law of denervation. Preganglionic denervation of the parasympathetic nerve supply to the submaxillary gland resulted in decreased sensitivity to ACh (15), and recently the secretory responsiveness to urecholine of the parasympathetic preganglionically denervated stomach (vagotomy) has been shown to be diminished (16). In all of these instances the mechanism is not known. It might be added that the mechanism of the increased sensitivity of most effectors is also unknown.

The diminished local sweating response to intracutaneously injected ACh in females as compared to males was described by Kahn and Rothman (9) and has recently been quantitated by Gibson and Shelley (17) for a standard dose of this drug. The evidence presented in the present study tends to indicate that this sex difference is not an absolute one but is due to differences in threshold.

The finding that the intensity of the axon reflex type of response increases as the concentration of ACh is raised, is not in conformity with the work of Rothman and co-workers. Their studies indicate that dilute solutions of ACh are more effective than concentrated ones in producing the axon reflex and they attribute this to the fact that this is a nicotinic type of response and, like the nicotine responses in autonomic ganglia, is inhibited by high concentrations of ACh. Our own studies have confirmed the nicotinic nature of the axon reflex sweating response to ACh by showing that, like the nicotinic stimulating effect in autonomic ganglia, it is blocked by tetraethylammonium (1). However, the present study indicates that the analogy between the autonomic ganglion and the point where ACH acts to produce axon reflex sweating breaks down in regard to optimal dosage. Unlike the autonomic ganglion, the receptor for axon reflex sweating shows no reversal of effect (i.e. inhibition) with increase in dosage. This is in keeping, however, with Coon and Rothman's failure to inhibit the axon response to locally injected nicotine by the parenteral administration of a large dose of drugs with nicotine-like action in both man and cat (18).

SUMMARY

1. The intracutaneous injection of acetylcholine esterase inhibitors, prostigmine and physostigmine, will induce sweating locally as well as potentiate the response to acetylcholine.

2. Postganglionically denervated sweat glands which do not respond to the local injection of a variety of parasympathomimetic drugs, alone and in mixtures, are capable of responding to intense local heat. Epinephrine, prostigmine, physostigmine, and histamine, when added to acetylcholine, fail to produce a sweat response in denervated glands.

3. The threshold dose of acetylcholine for locally induced sweating, and axon reflex sweating is higher in females than in males. The axon reflex type of sweating response is increased as the concentration of acetylcholine increases; high concentrations do not cause inhibition.

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