Effects of cholinomimetic drugs on sudomotor, metabolic, respiratory, vasomotor, and temperature response in palmar hyperhidrosis

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The effects of cholinomimetic drugs such as mecholyl (methacholine) and pilocarpine on autonomic functions (including sudomotor, metabolic, respiratory, vasomotor, and temperature responses) were assessed at room temperature (24°C) in three groups of individuals, including normal, hyperhidrotic, and denervated subjects. The normal group had no palmar hyperhidrosis, with intact T2-3 ganglia, the hyperhidrotic group had palmar hyperhidrosis with intact T2-3 ganglia, and the denervated group had palmar hyperhidrosis treated with T2-3 ganglionectomy. Subcutaneous administration of mecholyl and pilocarpine each produced a fall in oral temperature in the normal group. The hypothermia was brought about by a decrease in metabolic rate, an increase in local sweating rate (mainly of the upper limb and trunk), and an increase in cutaneous circulation (estimated by an increase in the upper limb and trunk skin temperatures). The autonomic functions induced by these cholinomimetic drugs were antagonized by pretreatment with atropine sulfate (an antagonist of cholinergic receptors). Moreover, the hypothermia induced by mecholyl or pilocarpine was greatly reduced in the hyperhidrotic group. The reduction in the cholinomimetic-induced hypothermia in the hyperhidrotic group was due to the reduced sudomotor and metabolic responses after the injections of these cholinomimetic drugs, as compared to those of the normal group. However, neither the excessive sweating of the palms nor the reduced cholinergic responses in the hyperhidrotic group was observed after T2-3 ganglionectomy. The data indicate that the T2-3 ganglia play a role in the elaboration or modulation of the sudomotor and metabolic responses induced by activation of certain cholinergic receptors in humans.

Key Words • brachial plexus • autonomic ganglion • nerve degeneration • neural pathway • sympathectomy • sweating • hyperhidrosis • autonomic system

It is well known that the efferent innervation of sweat glands, although anatomically sympathetic, is functionally cholinergic. In accordance with the neurohumoral concept of nervous excitation, acetylcholine is liberated at the sudomotor endings, and acts directly on the glands. Cholinesterase is present in high concentration in the nerve fibers about the secretory acini of the sweat glands.

During the 28 years up to 1978, 457 patients with palmar hyperhidrosis, suffering from excessive sweating of the palms, had sought surgical relief at our hospital. The total has now increased to 539 patients. It has been shown that the excessive sweating of the palms in these patients could be permanently abolished by T2-3 ganglionectomy.

The present study has attempted to assess the effects of cholinomimetic drugs, such as mecholyl (methacholine) and pilocarpine, on autonomic functions (including sudomotor, metabolic, respiratory, vasomotor, and temperature responses) in patients with palmar hyperhidrosis both before and after T2-3 ganglionectomy. This study was conducted in order to ascertain the nature of the contribution that the T2-3 ganglia might make in autonomic control.

Clinical Material and Methods

Experimental Groups

Experiments were performed on Chinese males, including six normal subjects, 10 patients with palmar

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hyperhidrosis, and 10 patients with T2-3 ganglionectomy. The subjects weighed between 55 and 65 kg, and were aged between 22 and 25 years. They were divided into three groups, as follows: Group 1: normal group; subjects who did not have excessive sweating of the palms and had intact T2-3 ganglia; Group 2: hyperhidrotic group; subjects who complained of excessive sweating of the palms and had intact T2-3 ganglia; and Group 3: denervated group; the same patients as in Group 2, after they had been treated with T2-3 ganglionectomy and had complete resolution of excessive sweating of the palms. The physiological responses of these groups of subjects to a subcutaneous dose of mecholyl were measured.

Surgical Technique

After control studies were made on Group 2 patients, these 10 patients were then operated on by the methods described previously. In brief, each patient was operated on through a dorsal approach. Both the proximal part of the third rib and the transverse process of the T-3 vertebra were resected subperiosteally. The gray and white communicating rami of the T-2 and T-3 ganglia were sectioned. The part of the sympathetic trunk above the T-2 ganglion and below the T-3 ganglion was also severed to permit complete removal of an entire piece of sympathetic chain containing the T2-3 ganglia. In all cases, the excised section was studied histologically to confirm the presence of ganglion cells in the specimen. Three weeks to 8 months after the operation, the subjects were subjected to experiments.

Drug Solutions

All drug solutions were prepared in pyrogen-free glassware which was baked at 180°C for 5 hours before use. Freshly prepared solutions were used for all injections. Drugs administered subcutaneously included mecholyl chloride (methacholine chloride, 10 mg); pilocarpine hydrochloride (10 mg); and atropine sulfate (0.5 mg).

Measurement of Physiological Parameters

Metabolic rate (M) was calculated from the subject's oxygen consumption in watts, assuming a respiratory quotient = 0.83, so that 1 liter of oxygen consumed per hour was equivalent to a heat production of 5.6 W. Respiratory evaporative heat loss (Ere) was calculated by measuring the increase in water vapor content in the helmet effluent air over that of the ambient air. Respiratory evaporative heat loss, expressed as watts, was calculated from evaporative water loss assuming the latent heat of the vaporization of water to be 0.7 W/hr/gm.

Local sweating rate (LSR) was measured from a skin area of 6.5 sq cm on each skin surface by a sweat-collection capsule. Local sweating rates were measured on different locations on the body surface, including the palm, upper arm, and ventral thigh.

Oral (To), palm skin (Tp), upper arm skin (Tt), upper chest (Te), and ventral thigh skin (Tt) temperatures were measured by means of thermocouples.

All the above-mentioned measurements, besides the LSR, were taken once per minute throughout the experiments, each variable being measured as a direct current potential on a Hewlett-Packard digital voltmeter (DVM 3455) and a scanner 3495 interfaced to an on-line CPU 9825 computer. Each minute all temperatures, metabolites, and evaporative heat loss were calculated instantaneously by the computer and relayed back to the laboratory where they were displayed by an on-line Hewlett-Packard printer 9871.*

Data Collection and Analysis

Subjects were permitted a period of at least 60 minutes at an ambient temperature of 24 ± 1.0°C to attain thermal balance before drug injection or the sweat collection capsule was mounted on the desired skin surface. Thirty minutes after the sweat capsule was mounted, it was removed and the inside contents with the filter paper were weighed. The maximal changes in Tt, Tp, To, Tc, Tr, M, and Ere produced within a 30-minute period after drug injection were expressed as ΔTo, ΔTp, ΔTt, ΔTc, ΔTr, ΔM, and ΔEre, respectively. Differences in the mean values of variables between the control and experimental groups were analyzed, using one-way analysis of variance.

Results

Table 1 summarizes the autonomic responses of three groups of normal, hyperhidrotic, and denervated subjects in response to a subcutaneous dose of mecholyl or pilocarpine at an ambient temperature of 24°C. The effects obtained with 10 mg mecholyl injected into the subcutaneous tissue in these groups of subjects are illustrated by the experiments of Figs. 1-3. In each experiment a control injection of 0.9% NaCl solution did not affect the autonomic responses studied. Subcutaneous administration of mecholyl and pilocarpine each produced a fall in oral temperature (Fig. 1 and Table 1). The hypothermia in response to mecholyl or pilocarpine was brought about by a decrease in metabolic rate, an increase in the cutaneous circulation (Fig. 1 and Table 1), and an increase in local sweating rate of upper limb and trunk (Table 2). For example, during the 30-minute period of the mecholyl-induced hypothermia, metabolic rate and local sweating rate (upper arm) were respectively 15 W/kg lower (Table 1) and 0.22 mg/sq cm/min

*Instruments manufactured by Hewlett-Packard Corp., 16399 West Bernardo Drive, San Diego, California.
TABLE 1

Autonomic responses to mecholyl and pilocarpine

<table>
<thead>
<tr>
<th>Groups of Subjects</th>
<th>No. of Subjects</th>
<th>$\Delta T_o$ (°C)</th>
<th>$\Delta M$ (W/kg)</th>
<th>$\Delta E_{res}$ (W/kg)</th>
<th>$\Delta T_e$ (°C)</th>
<th>$\Delta T_t$ (°C)</th>
<th>$\Delta T_p$ (°C)</th>
<th>$\Delta T_i$ (°C)</th>
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</thead>
<tbody>
<tr>
<td>mecholyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>6</td>
<td>-0.9 ± 0.08†</td>
<td>-15.0 ± 1.12†</td>
<td>0.2 ± 0.02</td>
<td>1.0 ± 0.14</td>
<td>1.0 ± 0.12</td>
<td>1.2 ± 0.35</td>
<td>-0.3 ± 0.12</td>
</tr>
<tr>
<td>hyperhidrotic</td>
<td>10</td>
<td>-0.5 ± 0.07†</td>
<td>-8.3 ± 0.93</td>
<td>0.1 ± 0.03</td>
<td>0.8 ± 0.08</td>
<td>0.8 ± 0.11</td>
<td>0.9 ± 0.31</td>
<td>0.2 ± 0.09</td>
</tr>
<tr>
<td>denervated</td>
<td>10</td>
<td>-1.1 ± 0.09†</td>
<td>-15.3 ± 1.04†</td>
<td>0.1 ± 0.03</td>
<td>0.8 ± 0.10</td>
<td>0.7 ± 0.08</td>
<td>1.0 ± 0.45</td>
<td>0.4 ± 0.18</td>
</tr>
<tr>
<td>pilocarpine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>6</td>
<td>-1.1 ± 0.09†</td>
<td>-18.0 ± 0.93†</td>
<td>0.2 ± 0.08</td>
<td>1.2 ± 0.12</td>
<td>0.9 ± 0.09</td>
<td>0.8 ± 0.14</td>
<td>0.2 ± 0.07</td>
</tr>
<tr>
<td>hyperhidrotic</td>
<td>6</td>
<td>-0.4 ± 0.06</td>
<td>-7.1 ± 0.68</td>
<td>0.2 ± 0.06</td>
<td>0.9 ± 0.11</td>
<td>1.0 ± 0.12</td>
<td>0.7 ± 0.09</td>
<td>0.3 ± 0.09</td>
</tr>
<tr>
<td>denervated</td>
<td>6</td>
<td>-1.0 ± 0.09†</td>
<td>-16.5 ± 0.98†</td>
<td>0.1 ± 0.06</td>
<td>0.8 ± 0.09</td>
<td>1.1 ± 0.13</td>
<td>0.9 ± 0.08</td>
<td>0.3 ± 0.06</td>
</tr>
</tbody>
</table>

*The changes in oral temperature ($\Delta T_o$), metabolic rate ($\Delta M$), respiratory evaporative heat loss ($\Delta E_{res}$), upper chest skin temperature ($\Delta T_t$), upper skin temperature ($\Delta T_p$), palm skin temperature ($\Delta T_p$), and ventral thigh skin temperature ($\Delta T_i$) produced within a 30-minute period after a subcutaneous injection of mecholyl (10 mg) or pilocarpine (10 mg) in normal, hyperhidrotic, and denervated subjects. The values are expressed as the mean ± standard error of the mean.

†Significantly different from corresponding control values (hyperhidrotic group), at $p < 0.05$ (one-way analysis of variance).

higher (Table 2) than the values taken during the period before the injection. There was no change in respiratory evaporative heat loss. Furthermore, in the normal group, the autonomic responses induced by these two cholinomimetic drugs were greatly antagonized by pretreatment with atropine sulfate (Table 3).

In the hyperhidrotic group, a significant reduction in either the mecholyl-induced or pilocarpine-induced hypothermia was observed, as compared to that of the normal group (Table 1 and Fig. 2). This was primarily due to the reduced metabolic and sudomotor responses after the injection of these cholinomimetic drugs, as compared to those of the normal group (Tables 1 and 2). After a subcutaneous dose of 10 mg mecholyl, the metabolic rate decreased by only 8.3 W/kg and local sweating rate (upper arm) increased...
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**TABLE 2**

<table>
<thead>
<tr>
<th>Groups of Subjects</th>
<th>No. of Subjects</th>
<th>Local Sweating Rate (mg/sq cm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Palm</td>
<td>Upper Arm</td>
</tr>
<tr>
<td>mecholyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>6</td>
<td>$0.10 \pm 0.01$</td>
</tr>
<tr>
<td>hyperhidrotic</td>
<td>10</td>
<td>$0.04 \pm 0.01$</td>
</tr>
<tr>
<td>denervated</td>
<td>10</td>
<td>$0.11 \pm 0.01$</td>
</tr>
<tr>
<td>pilocarpine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>6</td>
<td>$0.12 \pm 0.02$</td>
</tr>
<tr>
<td>hyperhidrotic</td>
<td>6</td>
<td>$0.05 \pm 0.01$</td>
</tr>
<tr>
<td>denervated</td>
<td>6</td>
<td>$0.13 \pm 0.02$</td>
</tr>
</tbody>
</table>

*The changes in local sweating rate of palm, upper arm, and ventral thigh produced within a 30-minute period after a subcutaneous injection of mecholyl (10 mg) or pilocarpine (10 mg) in normal, hyperhidrotic, and denervated subjects. The values are expressed as the mean ± standard error of the mean.

~Significantly different from corresponding control values (hyperhidrotic group), at $p < 0.05$ (one-way analysis of variance).

Discussion

Mecholyl (methacholine) and pilocarpine are closely related chemically to acetylcholine, and it is believed that they exert characteristic actions in a similar manner. However, they are less readily hydrolyzed by cholinesterase, and thus have a longer duration of action. In the present study, systemic administration of mecholyl and pilocarpine each produced a fall in oral temperature in normal adults. The hypothermia in response to these two cholinomimetic drugs was brought about by a decrease in metabolic

**FIG. 3.** The changes in oral temperatures ($T_o$), metabolic rate ($M$), palm skin temperature ($T_p$), upper arm skin temperature ($T_r$), ventral thigh skin temperature ($T_t$), upper chest skin temperature ($T_c$), and respiratory evaporative heat loss ($E_{res}$) produced by a subcutaneous injection of mecholyl in the same hyperhidrotic patient as depicted in Fig. 2, 6 weeks after T2-3 ganglionectomy.

**TABLE 3**

The effects of atropine sulfate treatment on hypothermia induced by mecholyl and pilocarpine in normal adults*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Subjects</th>
<th>Changes in Oral Temperature ($^\circ C$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% saline + mecholyl 10 mg</td>
<td>6</td>
<td>$-1.0 \pm 0.08$</td>
</tr>
<tr>
<td>atropine sulfate 0.5 mg</td>
<td>6</td>
<td>$-0.1 \pm 0.07$</td>
</tr>
<tr>
<td>atropine sulfate 0.5 mg + mecholyl 10 mg</td>
<td>6</td>
<td>$-0.2 \pm 0.06$†</td>
</tr>
<tr>
<td>0.9% saline + pilocarpine 10 mg</td>
<td>6</td>
<td>$-1.2 \pm 0.09$†</td>
</tr>
<tr>
<td>atropine sulfate 0.5 mg + pilocarpine 10 mg</td>
<td>6</td>
<td>$-0.3 \pm 0.05$‡</td>
</tr>
</tbody>
</table>

*The values are expressed as the mean ± standard error of the mean. Treatment was by subcutaneous injection.

†Significantly different from control values (saline + mecholyl group) at $p < 0.05$ (one-way analysis of variance).

‡Significantly different from control values (saline + pilocarpine group) at $p < 0.05$ (one-way analysis of variance).
rate, an increase in local sweating rate (mainly of the upper limbs and trunk), and an increase in cutaneous circulation (as estimated by an increase in the skin temperatures of the upper chest, upper arm, and palm) at room temperature (24°C). There was no change in respiratory evaporative heat loss. Furthermore, hypothermia induced by mecholyl or pilocarpine was antagonized by pretreatment with atropine sulfate (a specific antagonist of cholinergic receptors). The data indicate that activation of cholinergic receptors with mecholyl or pilocarpine decreases heat production and increases heat loss, which leads to hypothermia in humans. The present results are consistent with the experimental findings of List and Peet, who also found that administration of mecholyl or pilocarpine produced sweating in humans.

Perhaps the most striking aspect of the present results is that hypothermia induced by both mecholyl and pilocarpine was greatly reduced in patients with palmar hyperhidrosis. This reduction was due to the reduced sudomotor and metabolic responses after the injections of mecholyl or pilocarpine as compared to those of normal subjects. Furthermore, neither the excessive sweating of the palms of the hands nor the reduced cholinoimetic-induced autonomic responses was observed after the surgical removal of the T2–3 ganglia. Indeed, the present results show that the sudomotor, metabolic, and temperature response induced by mecholyl or pilocarpine in hyperhidrotic patients was greatly enhanced after T2–3 ganglionectomy. The present results are consistent with the findings of Peet and List. These investigators also reported that the sudomotor response to both pilocarpine and mecholyl was enhanced following the destruction of the intermediolateral column or section of the preganglionic fibers outside the spinal cord. Thus, it appears that the T2–3 ganglia play a role in the elaboration or modulation of the sudomotor, metabolic, and temperature responses induced by activation of certain cholinergic receptors in humans.

To our knowledge, palmar hyperhidrosis is a condition where excessive sweating of the palms occurs without an obvious etiology. The composition of sweat and morphological appearance of the sweat glands in palmar hyperhidrosis have been examined and no abnormalities have been found. However, in 1969, Cloward proposed a hypothesis to explain the condition based on abnormalities of cerebral cortical areas where somatotopic representation of sweating is present. An abnormality (hyperfunction) in the sudomotor fibers descending from the cerebral cortical areas associated with sweating of the palms and passing through the second or third paravertebral sympathetic ganglion is thought to be the cause of palmar hyperhidrosis. In addition, it has been demonstrated that the cessation of sweating in circumscribed areas of the skin, due to sympathetic denervation, is often associated with a compensatory hyperhidrosis in surrounding zones. Thus, it is likely that the excessive sweating of the palms may induce an afferent inhibitory input that leads to an abnormality in the cerebral cortical areas where sweating of the other parts (beside the palms) of the body is somatotopically represented. Accordingly, an abnormality (hypofunction) in the sudomotor fibers descending from these cerebral cortical areas concerned with sweating of other parts of body would account for the reduced sudomotor response to the cholinoimetic drugs in hyperhidrotic patients. Surgical removal of the T2–3 ganglia could result in the postoperative reduction of LSR in the palms and the postoperative abolition of the reduced cholinergic responses as demonstrated in our series. Of course, this hypothesis needs further verification.

It is well known that the neurohumoral transmitter of all preganglionic autonomic fibers, all postganglionic parasympathetic fibers, and a few postganglionic sympathetic (such as, sudomotor) fibers is acetylcholine. Drugs that stimulate autonomic ganglia at cholinoceptive sites can be grouped into two major categories: those with nicotinic and those with muscarinic actions. In the present study, it was found that both mecholyl and pilocarpine act on the muscarinic receptors, since their actions have been antagonized by pretreatment with atropine.

References

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