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Pilocarpine-induced sweat gland function in individuals with multiple sclerosis

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Davis, Scott L., Thad E. Wilson, Jamie M. Vener, Craig G. Crandall, Jack H. Petajan, and Andrea T. White. Pilocarpine-induced sweat gland function in individuals with multiple sclerosis. *J Appl Physiol* 98: 1740–1744, 2005. First published January 7, 2005; doi:10.1152/jappphysiol.00860.2004.—This investigation tested the hypothesis that cholinergic sweat function of individuals with multiple sclerosis (MS) (MS-Con; $n = 10$) is diminished relative to matched healthy control subjects (Con; $n = 10$). In addition, cholinergic sweat function was determined before and after 15 wk of aerobic training in a subgroup of individuals with MS (MS-Ex; $n = 7$). Cholinergic sweating responses were assessed via pilocarpine iontophoresis on ventral forearm skin. A collection disk placed over the stimulated area collected sweat for 15 min. Sweat rate (SR) was calculated by dividing sweat collector volume by collection area and time. Iodine-treated paper was applied to the stimulated area to measure number of activated sweat glands (ASG). Sweat gland output (SGO) was calculated by dividing SR by density of glands under the collector. Sweat gland function was determined in MS-Ex to test the hypothesis that exercise training would increase sweating responses. No differences in ASG were observed between MS-Con and Con. SR and SGO in MS-Con [$0.18 \text{ mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ (SD 0.08); $1.74 \mu\text{g}\cdot\text{gland}^{-1}\cdot\text{min}^{-1}$ (SD 0.79), respectively] were significantly lower ($P \leq 0.05$) than in Con [$0.27 \text{ mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ (SD 0.10); $2.43 \mu\text{g}\cdot\text{gland}^{-1}\cdot\text{min}^{-1}$ (SD 0.69)]. Aerobic exercise training significantly ($P \leq 0.05$) increased peak aerobic capacity in MS-Ex [1.86 (SD 0.75) vs. 2.10 (SD 0.67) l/min] with no changes in ASG, SR, and SGO. Sweat gland function in individuals with MS is impaired relative to healthy controls. Fifteen weeks of aerobic training did not increase stimulated sweating responses in individuals with MS. Diminished peripheral sweating responses may be a consequence of impairments in autonomic control of sudomotor function.

sweat rate; sweat gland density; demyelination; sudomotor

MULTIPLE SCLEROSIS (MS) is a demyelinating disease of the central nervous system that can disrupt autonomic pathways, leading to impaired control of thermoregulatory function (7). Sixty to 80% of the MS population experiences transient increases in the frequency or severity of clinical signs and symptoms (i.e., fatigue, spasticity) as a result of elevated body temperature (26). Individuals with MS may be susceptible to nerve conduction block with relatively small increases (i.e., as little as 0.5°C) in core body temperature (8, 21). Compounding existing temperature-related nerve conduction problems, areas of diminished sweating have been qualitatively identified in

MS patients (17, 27), and impaired sweat function has been reported more frequently in patients with more severe cases of MS (5). In the aforementioned studies, abnormal sweating responses were identified by using a technique in which quinizarin powder is placed on the skin of individuals followed by exposure to a heat stress. Quinizarin powder, normally gray in color, changes to a deep blue when exposed to sweat. The intensity of the change in color gives a visual estimate of sweating (12). However, this technique cannot quantitatively identify differences in sweating or whether diminished sweating is due to a decreased number of active sweat glands and/or reduced output from activated glands.

A simple test using a supramaximal concentration of an intradermal cholinergic agent (pilocarpine) can provide relevant quantitative measures of sweat gland function (23). Pilocarpine stimulates muscarinic receptors on eccrine sweat glands, which are innervated by postganglionic cholinergic nerve fibers. Local administration of pilocarpine is useful in characterizing sweat gland function independent of central nervous system control (11).

Despite growing evidence suggesting that physical activity is beneficial in the treatment of MS, many individuals with the disease (especially those with more severe cases of MS) remain sedentary (16). Avoiding physical activity can decrease the reliance on sweating as a heat dissipation mechanism, leading to further reductions in sweat gland function (14). Compromised sweat function observed in MS patients may be peripheral in origin due to decreased physical activity rather than a result of the central nervous system disorder. Aerobic training has been shown to improve the secretory activity of human sweat glands (14, 22). For example, peripheral sweat production induced by pilocarpine iontophoresis was significantly greater in both healthy trained men and women compared with healthy untrained counterparts (3). Furthermore, peripheral sweat rate was significantly correlated with maximal oxygen uptake (3). Therefore, physical activity may be a viable intervention to increase sweat production and thereby increase heat tolerance in individuals with MS.

The first goal of the present investigation was to test the hypothesis that the number of activated sweat glands and sweat production in individuals with MS is reduced relative to healthy control subjects after cholinergic stimulation. A second goal of the investigation was to test the hypothesis that aerobic

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exercise training improves sweat gland function in MS patients.

METHODS

Protocol 1: Comparison of Sweating Characteristics in Individuals With MS and Controls Subjects

Participants. Ten women with MS, recruited through physician referrals, comprised the MS group (MS-Con) (Table 1). Participants were selected on the basis of the following criteria: definite clinical diagnosis of MS, Kurtzke expanded disability status scale (EDSS) score between 3.0 and 6.0, and no history of cardiovascular, respiratory, orthopedic, metabolic, or other medical condition that would preclude participation in an aerobic training program (13, 20). Ten women with no diagnosis of MS, matched to MS participants by age, height, weight, and peak aerobic capacity ($\dot{V}O_{2\text{ peak}}$), were recruited and assigned to the control group (Con) (Table 1). Participants provided written, informed consent approved by the Institutional Review Board of the University of Utah.

Neurological evaluation. A neurological evaluation was performed on participants with MS by a board-certified neurologist specializing in MS before the beginning of the study. A thorough medical history was recorded, and participants were evaluated utilizing components of the MS minimal record of disability forms (neurological examination, incapacity status scale, Kurtzke's functional system scales) and Kurtzke EDSS (13, 15). All individuals with MS reported existing heat sensitivity to one or more of the following conditions: high ambient temperature, high water temperature, and/or physical activity.

Exercise testing. $\dot{V}O_{2\text{ peak}}$ was measured by a maximal graded exercise test performed on an air-resistance arm and leg cycle ergometer (Schwinn Air-Dyne, Boulder, CO). Four different testing protocols were used to provide appropriate workloads for individuals with varying work capacities. Participants began at a work rate of 15, 25, or 40 W with the work rate increasing 10 to 40 W every 1–2 min. During the test, oxygen consumption, respiratory exchange ratio (RER), and ventilation were recorded every 20 s via open-circuit indirect calorimetry (True Max 2400, ParvoMedics Murray, UT). Heart rate was obtained throughout the test with rating of perceived exertion (RPE) recorded after each stage and at test termination. The test was terminated when one or more of the following criteria had been met: 1) any symptoms that impaired the individual's ability to continue or indicated a risk to safety or health, 2) volitional exhaustion, or 3) RER >1.0.

Pilocarpine iontophoresis. Peripheral sweat production was induced by pilocarpine iontophoresis to the ventral side of the forearm, 3–4 cm distal to the antecubital space (2, 3). Individuals in MS-Con were tested on a symptomatic forearm identified during the neurological evaluation (Table 2). Individuals in Con were tested on the right forearm.

Pilocarpine (0.5% pilocarpine nitrate in solid agar gel) was iontophored by using a Webster sweat inducer (model 3700, Wescor, Logan, UT) to elicit maximal sweating (28). Two complete cycles of iontophoresis (each cycle equivalent to 5.5 min at 1.5 mA) were performed. An environmentally sealed sweat collection disk (Macroduct sweat collection system, Wescor) was placed over the stimulated area to collect sweat for 15 min. After sweat collection, iodine-

Table 2. Forearm tested and neurological involvement in individuals with multiple sclerosis

MS-Con Subject No.	Forearm Tested	Neurological Involvement
1	Right	Sensory deficit
2*	Left	Coordination impairment, weakness, sensory deficit
3*	Right	Coordination impairment, weakness, sensory deficit
4	Right	Weakness
5*	Right	Sensory deficit
6	Right	Coordination impairment
7*	Left	Coordination impairment, weakness, sensory deficit
8*	Right	Coordination impairment, weakness, sensory deficit
9*	Right	Coordination impairment, weakness, sensory deficit
10*	Left	Weakness, sensory deficit

*Individuals also in MS-Ex subgroup.

treated linen paper with 1-cm grids was applied to the stimulated area for ~15–20 s and then scanned into a computer. Imaging software (NIH Image) was used to calculate the number of activated sweat glands per square centimeter (ASG). Total sweat volume was measured from pre- and postcollector weights. Sweat rate (SR) was calculated by dividing volume of sweat in the collector by the collector area (6.413 cm²) and time of collection (15 min). Sweat gland output (SGO) was calculated by dividing SR by the density of glands under the collector.

Protocol 2: Effect of Training on Sweating Characteristics in Individuals with MS

Seven individuals from MS-Con agreed to participate in a supervised 15-wk exercise training program, which comprised the MS exercise group (MS-Ex) (Table 1). The individuals provided written consent to participate and were informed of their rights as outlined by the Institutional Review Board of the University of Utah. The training program was previously described by Petajan et al. (18). Individuals in the MS-Ex group participated in three supervised training sessions per week in the laboratory at an ambient temperature of 22°C. Training was performed on the same type of air resistance arm and leg cycle ergometer used during the graded exercise test. Each training session consisted of a 5-min warm-up at 30% of $\dot{V}O_{2\text{ peak}}$, 30 min of exercise at 60% $\dot{V}O_{2\text{ peak}}$, and a 5-min cooldown at 30% of $\dot{V}O_{2\text{ peak}}$. Initial training work rates were calculated on the basis of the results of the oxygen consumption-workload relationship obtained during the initial pretraining graded exercise tests (Base). An additional graded exercise test was performed at 7 wk using the same graded exercise testing protocol as described previously. Training work rates were adjusted based on results from this graded exercise test. After 15 wk, each participant completed a final graded exercise test. A second neurological evaluation was performed at the conclusion of the study (Wk15) on each MS-Ex individual. Data obtained from the initial neurological evaluations (Base) were compared with posttraining evaluations to track changes in neurological status during the training period. Peripheral sweat production after the training program was induced by the iontophoresis procedure previously described. Post-

Table 1. Participant characteristics

Group	n	Age, yr	Height, cm	Weight, kg	$\dot{V}O_{2\text{ peak}}$, ml·kg ⁻¹ ·min ⁻¹	EDSS	EDSS Range
Con	10	44.0 (9.1)	166.8 (7.3)	77.3 (23.7)	26.9 (6.9)	NA	NA
MS-Con	10	44.7 (8.0)	165.8 (7.1)	70.8 (16.1)	26.0 (5.9)	5.2 (1.3)	3.0–6.5
MS-Ex	7	44.4 (7.4)	169.4 (6.8)	75.5 (17.1)	25.0 (7.0)	4.4 (1.5)	3.0–6.0

Values are means (SD); n, no. of subjects. $\dot{V}O_{2\text{ peak}}$, peak aerobic capacity; Con, control subjects; MS-Con, individuals with multiple sclerosis; MS-Ex, subgroup of Ms-Con who participated in a 15-wk exercise training program; EDSS, expanded disability scale score; NA, not applicable.

Table 3. Peak physiological variables for Con and MS-Con during maximal graded exercise testing

	Con	MS-Con	P Value
$\dot{V}O_{2\text{ peak}}$, ml·kg ⁻¹ ·min ⁻¹	26.9 (6.9)	26.0 (5.9)	0.770
Peak heart rate, beats/min	172.2 (13.8)	166.2 (15.7)	0.376
Respiratory exchange ratio	1.10 (0.09)	1.07 (0.06)	0.284
Rating of perceived exertion	18.2 (1.7)	17.3 (1.9)	0.461

Values are means (SD).

training ASG, SR, and SGO were identified and compared with pretraining values.

Statistical Analysis

Unpaired *t*-tests were performed on ASG, SR, and SGO comparing MS-Con and Con groups. Paired *t*-tests were used to compare Base and Wk15 differences in $\dot{V}O_{2\text{ peak}}$, SR, ASG, and SGO in the MS-Ex

group. Statistical significance was accepted at $P \leq 0.05$. All values are expressed as means \pm SD.

RESULTS

Protocol 1: Comparison of Sweating Characteristics in Individuals with MS and Con

No differences were observed in $\dot{V}O_{2\text{ peak}}$, peak heart rate, RER, or RPE between MS-Con and Con at the termination point of the maximal graded exercise test (Table 3). No differences were observed in ASG (Fig. 1A) between MS-Con [106.3 glands/cm² (SD 15.7)] and Con [109.5 glands/cm² (SD 20.3)]. SR (Fig. 1B) for MS-Con [0.18 mg·cm⁻²·min⁻¹ (SD 0.08)] was significantly lower ($P \leq 0.05$) than Con [0.27 mg·cm⁻²·min⁻¹ (SD 0.10)]. Similarly, SGO (Fig. 1C) was also significantly lower ($P \leq 0.05$) in MS-Con [1.74 $\mu\text{g}\cdot\text{gland}^{-1}\cdot\text{min}^{-1}$ (SD 0.79)] compared with Con [2.43 $\mu\text{g}\cdot\text{gland}^{-1}\cdot\text{min}^{-1}$ (SD 0.69)].

Protocol 2: Effect of Training on Sweating Characteristics in Individuals With MS

All seven MS-Ex participants completed the training protocol with no changes in neurological status. Clinical and treatment status remained unchanged throughout the training period. Fifteen weeks of aerobic training significantly increased ($P \leq 0.05$) $\dot{V}O_{2\text{ peak}}$ (Table 4, Fig. 2). However, exercise training did not alter ASG, SR, or SGO (Table 4, Fig. 2).

DISCUSSION

The primary finding of this study is that both SR and SGO were significantly reduced in untrained individuals with MS compared with similarly inactive control subjects. No differences were observed in the number of active sweat glands in individuals with MS were responsive to pilocarpine administration compared with healthy controls. These results are in agreement with Vas (27), who suggested that postganglionic sympathetic nerves and sweat glands were responsive to peripheral cholinergic stimulation in individuals with MS. These results suggest that diminished sweat function observed in individuals with MS is due to reduced SGO rather than diminished sweat gland recruitment. By carefully matching each individual with MS to a healthy control with similar $\dot{V}O_{2\text{ peak}}$, initial cardiorespiratory fitness did not impact the observed differences in sweat function between groups.

Diminished areas of sweating in individuals with MS were previously visually identified by using quinazarin powder ap-

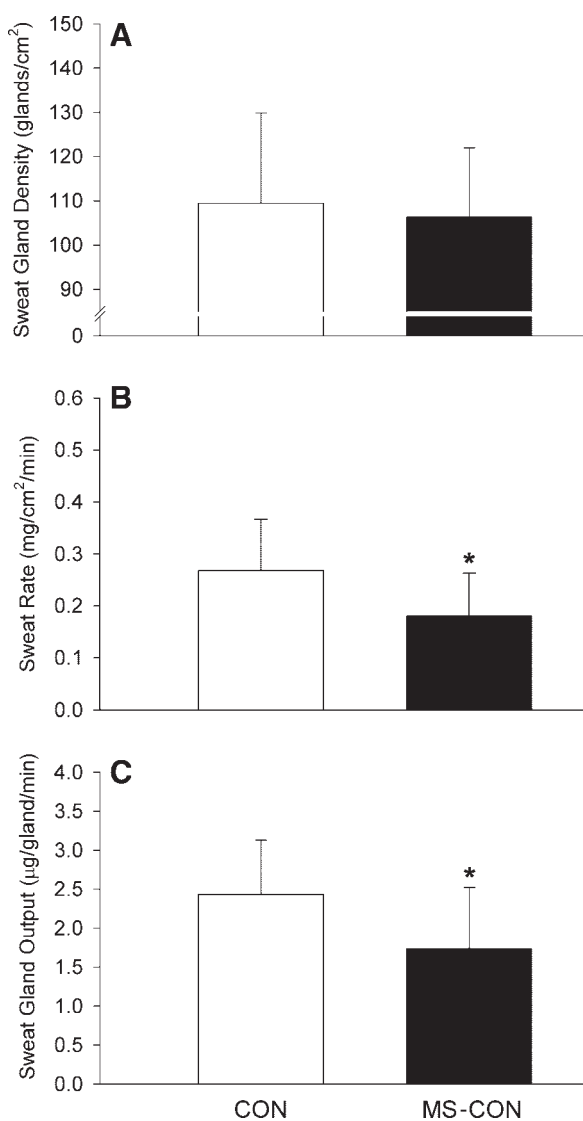


Fig. 1. A: activated sweat gland density (ASG) comparing individual with multiple sclerosis (MS-Con) and healthy control subjects (Con). B: sweat rate (SR) comparing MS-Con and Con. C: sweat gland output (SGO) comparing MS-Con and Con. Solid bars, MS-Con; open bars, Con. Values are means \pm SD. *Significantly different from Con, $P < 0.05$.

Table 4. Effects of 15 wk of aerobic exercise training on aerobic capacity, sweat gland density, sweat rate, and sweat gland output in individuals with multiple sclerosis

	Base	Wk15	P Value
$\dot{V}O_{2\text{ peak}}$, l/min	1.86 (0.75)	2.10 (0.67)*	0.025
Activated sweat gland density (ASG), gland/cm ²	106.3 (18.2)	109.8 (20.6)	0.365
Sweat rate, mg·cm ⁻² ·min ⁻¹	0.18 (0.10)	0.19 (0.10)	0.442
Sweat gland output, $\mu\text{g}\cdot\text{gland}^{-1}\cdot\text{min}^{-1}$	1.68 (0.90)	1.86 (1.08)	0.357

Values are means (SD) for 7 subjects in MS-Ex group. Base, pretraining; Wk15, after 15 wk of aerobic exercise training. * $P \leq 0.05$ vs. Base values.

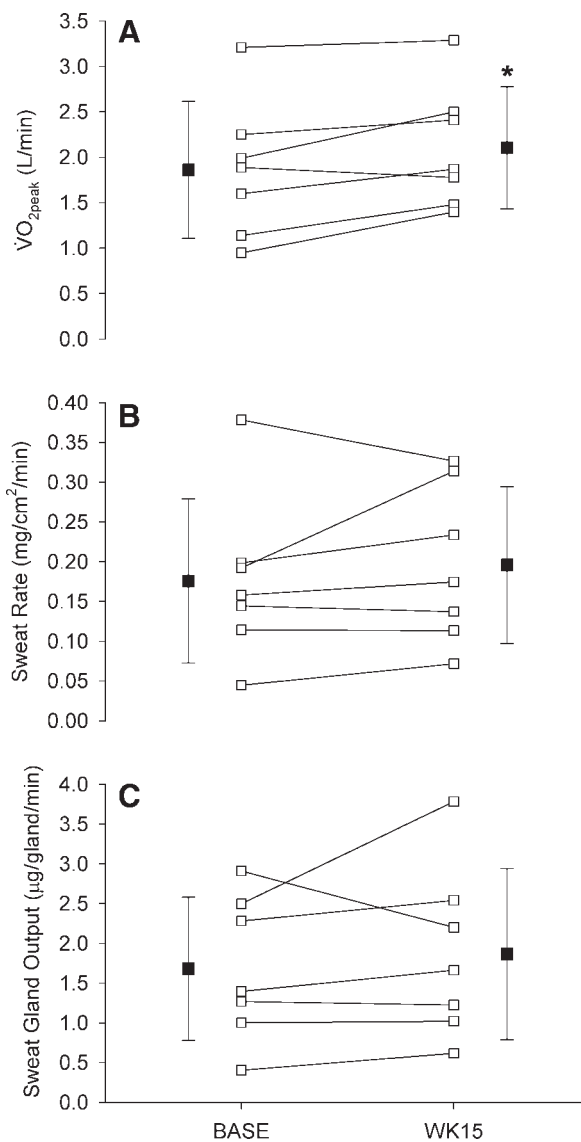


Fig. 2. Mean responses \pm SD (■) and individual responses (□ with lines) for peak aerobic capacity ($\dot{V}O_{2\text{peak}}$; A), sweat rate (SR; B), and sweat gland output (SGO; C) before (Base) and after 15 wk (Wk15) of aerobic exercise training. *Significantly different from Base, $P < 0.05$.

plied to the skin during a passive heat stress (5, 17, 27). This technique does not separate central (i.e., neural) from peripheral (i.e., sweat gland) abnormalities. Therefore, local administration of pilocarpine, a cholinergic agent, was used in this study to evaluate and quantify peripheral sweat gland function (activated glands and sweat production) independent of central nervous system control (11).

Although growing evidence demonstrates the benefits of physical activity in the management of MS, many individuals with the disease remain sedentary (16, 19, 29). Complete inactivity (14 days of bed rest) has been shown to decrease maximal acetylcholine-induced sweat rate without altering the number of activated sweat glands (6). Decreased reliance on sweating as a heat dissipation mechanism leads to changes in the sweat gland, including reduced gland size and decreased cholinergic sensitivity (24). Conversely, maximal cholinergic sweat function is preserved in individuals who exercised

throughout bed rest (6). Training has been shown to improve the secretory activity of the human sweat gland independent of neural control in healthy subjects (2–4, 10). Therefore, it was hypothesized that exercise training might be a viable intervention for increasing cholinergic sensitivity and glandular output in individuals with MS. Although a significant increase in aerobic capacity was attained, SR and SGO were unchanged in individuals with MS after 15 wk of aerobic training.

Individuals exercised on an air-resistance ergometer that produced greater air movement with increasing work rate. This air movement could have cooled individuals during exercise, thereby decreasing the thermal stimulus. However, our previous work with individuals with MS utilizing an identical training protocol in similar ambient conditions resulted in an average core temperature increase of 1.0°C during the 40-min exercise bout (29). This magnitude of thermal stimulus induced via exercise has previously been shown to produce adaptations in sweat function (22). In addition, Sawka et al. (25) suggested that exercise training intensities should exceed 50% maximal oxygen uptake for >1 wk for thermoregulatory adaptations to occur, with optimal adaptations occurring in 8–12 wk. The present study's exercise training regime is comparable to these guidelines (i.e., 60% $\dot{V}O_{2\text{peak}}$ for 15 wk). We cannot exclude the possibility that adaptations in sweating could be observed with higher intensity and/or duration training. However, increasing intensity and/or duration of training sessions in this population is difficult because of acute exercise-induced worsening of clinical symptoms.

Areas of the sympathetic nervous system (hypothalamic area and posterior tract of the spinal cord) that control thermoregulatory functions are susceptible to demyelination in individuals with MS (24). Diminished sweat function observed in MS patients, while peripheral in origin, are suggestive of central nervous system impairments causing conduction abnormalities and even neuronal loss within the descending sudomotor pathways due to the disease (1, 27). This insufficient sympathetic input to sweat glands could lead to peripheral adaptations such as 1) reduced cholinergic sensitivity, 2) downregulation of muscarinic receptors, and/or 3) atrophy of sweat glands contributing to the diminished SR and SGO observed in this study. Central nervous system impairments may also account for the minimal peripheral sweat gland adaptations observed after exercise training in MS patients.

Limitations

Despite no significant increases in cholinergic sweat function after exercise training in this study, four of seven individuals in MS-Ex demonstrated small increases in SR after exercise training. Pilocarpine iontophoresis is an index of maximal cholinergic sweating and may not be reflective of exercise SR or less than maximal SR (9). It remains unclear whether exercise training in individuals with MS could improve sweat function during exercise or during passive heat exposure. This warrants further investigation. Regardless of the lack of improvement in maximal sweat function, exercise training should be encouraged as a therapeutic strategy in the management of the disease given the positive physiological and psychological benefits to individuals with MS (18).

Summary and Conclusions

Individuals with MS have diminished sweat gland function compared with healthy control subjects. Improvements in heat dissipation mechanisms such as sweating could be beneficial to individuals with MS by maintaining a safe core temperature and decreasing heat related signs and symptoms. Moreover, 15 wk of aerobic exercise training did not evoke any changes in sweat gland function in individuals with MS. If sweat function cannot be improved through exercise training, strategies to avoid excessive heat exposure, such as cooling or precooling, must be emphasized to individuals with MS.

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