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19. Abstract (Cont'd)

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Human temperature regulation during exercise after
oral pyridostigmine administration

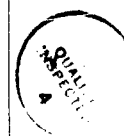
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Abstract

Four healthy males exercised in two experiments at ambient temperatures of 22°C, 29°C and 36°C. The relative humidity was 30% in each environment. One experiment in each environment was done 150 minutes after oral (30 mg) pyridostigmine bromide (PYP) administration, and the second experiment was done on a separate day with no medication (CON). Red blood cell cholinesterase was -39 (± 7)% lower after PYP (11.8 vs. 7.2 $\mu\text{mol}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$). Esophageal (T_{es}) and mean skin temperature (T_{sk}), forearm blood flow (FBF), forearm sweating, and skin blood flow (SkBF) were measured twice each minute during a 15 min rest period and during 30 minutes of seated cycle exercise at $\sim 58\% \dot{V}\text{O}_2$ peak. Whole body sweating was determined from weight changes before and after exercise. PYP decreased heart rate at rest and during exercise at 29°C and 36°C (8 bpm, $p < 0.05$). Resting SkBF was 40% lower at 29°C and 30% lower at 36°C after PYP. During exercise, SkBF was 40% lower at 29°C and 50% lower at 36°C after PYP compared to CON ($p < 0.05$). There was no effect of PYP on heat production at rest or during exercise. T_{sk} was different in the three conditions by design, but was unchanged by PYP. T_{es} was not different at rest in any condition, but was elevated during exercise at 36°C (0.1°C, $p < 0.05$) in PYP compared to CON. These data suggest that pyridostigmine ingestion decreased skin blood flow and limited thermoregulation by decreasing dry heat loss.

Running Title: Anticholinesterase and heat loss

Pyridostigmine, a carbamate, is a reversible anticholinesterase with a half-life of approximately 2.5 hours (3,18). Pyridostigmine and other anticholinesterases exert their action(s) at cholinergic synapses, as acetylcholine which is released upon neural stimulation, is not hydrolyzed and continues to bind with available receptors in the synaptic area (17,18,19). Individuals taking pyridostigmine or similar medications may experience increased salivation, sweating or bradycardia, which may affect an individual's ability to withstand exposure to severe environments. Pyridostigmine is used routinely in the clinical management of myasthenia gravis (18), and is used by the Armed Forces as a pretreatment drug given to soldiers who may subsequently be exposed to, or are under the threat of, exposure to nerve agent.

Exposure to environmental temperature extremes and/or increasing deep body temperature during exercise is associated with increased sweat gland secretion and vasodilation of surface vessels to transfer heat from the body core to the surface and subsequently to the environment (13,14). The sweat glands are innervated primarily by cholinergic fibers, although sweating can be induced through adrenergic stimulation (15). Skin and muscle blood flow are believed to have cholinergic components as well (6,13,14). Thus, any change in effector stimulation (sweat glands or vasomotor elements) which may result from increased cholinergic activity after pyridostigmine treatment may affect heat dissipation or perhaps body fluid status.

The present study characterized changes in thermoregulatory function at rest and during moderate, short term exercise following a single 30 mg oral dose of pyridostigmine bromide. The 30 mg dose was selected as it is

the dose contained in one tablet given to military personnel facing nerve agent exposure. We characterized temperature regulation in three environments which were chosen to provide three distinct mean skin temperatures at rest; one which was associated with significant vasoconstrictor activity; the second, which was in the thermal neutral or comfort zone, and a third which was associated with active vasodilation. Since skin temperature influences sweat gland secretion and vasomotor activity, studying the effects of cholinesterase inhibition on sweating and vasomotor function at different skin temperatures provided a thorough representation of drug effects.

Methods

Four healthy adult males participated in this study following approval by the human subjects review board. The mean ($\pm$ SD) age was 22 (± 4) years, height 175.4 (± 10.2) cm, weight 75.5 (± 5.4) kg and peak aerobic power 3.37 (± 0.45) L $\cdot$ min $^{-1}$. Each subject was tested on two separate test days in each of three different environments. The three environments were 22°C, 29°C, and 36°C. All tests were conducted at the same time of day to minimize the circadian variability in heat loss (16). The order of experiments was balanced for both environment and drug. On three test days, the subject came into the laboratory at 0700 h having not eaten or consumed caffeine containing beverages the previous 12 h, and ingested 30 mg pyridostigmine bromide (PYR, Roche UK, Lot BK94626) with 200 ml spring water. Immediately preceding and at 150 min after receiving the medication, red cell cholinesterase activity was determined (8). Red cell cholinesterase activity was also measured on the three control days (CON) at the same time of day as in PYR. Immediately after the second cholinesterase

determination (150 minutes post drug) or at the same clock time on control days, the subject swallowed a catheter containing a thermocouple into his esophagus for the measurement of core temperature. The thermocouple was inserted 25% of the subject's height and adjusted to a point at which the highest temperature was recorded. The use of esophageal temperature in these studies was critical as this site is the only one routinely used which responds very quickly and closely mimics changes in blood temperature. We routinely observe a rapid increase in esophageal temperature at the beginning of exercise and use this increase to evaluate changes in sudomotor and vasomotor responses (10). Eight surface thermocouples were taped to the skin to calculate a mean weighted skin temperature as:

$$T_{sk} = 0.07 T_{forehead} + 0.175 T_{chest} + 0.175 T_{back} + 0.07 T_{upperarm} + 0.07 T_{forearm} + 0.05 T_{hand} + 0.19 T_{thigh} + 0.20 T_{calf} \quad (12)$$

Forearm blood flow (FBF) was measured by venous occlusion plethysmography as described previously (9,20). Briefly, the forearm was suspended at the wrist with a sling anchored at two points, thereby minimizing movement artifact as the arm and strain gauge moved in translation with the torso. Blood flow from the hand was not measured as the wrist cuff was inflated to exceed systolic pressure. The measurement of FBF included flow through the skin, muscle, adipose tissue and bone. Cutaneous vascular perfusion was measured as an index of skin blood flow (SkBF) by laser doppler velocimetry (MED PACIFIC). This system used a 2 mW HeNe laser and fiber optic system to measure blood flow through the skin

of the forearm. The flow measurements reported are mV values which are proportional to the quantity of moving red blood cells multiplied by the average velocity of the red blood cells within the sample volume of the capillary tissue measured. Laser probe and strain gauge (for FBF) placement were identical for each experiment for each subject. Forearm sweating was measured on the contralateral forearm using a ventilated dew-point sensor attached firmly to the skin (7). This sensor was ventilated with ambient air from the chamber at a flow rate of $600 \text{ mL} \cdot \text{min}^{-1}$ which did not artificially dry the skin under the capsule, but allowed sufficient evaporation. Heart rate was measured from standard chest leads. Oxygen consumption was measured at rest and frequently during exercise (SENSORMEDICS). The percent change in plasma volume was calculated from hematocrit and hemoglobin measurements from blood samples taken at rest and during steady-state exercise (20 minutes) from an indwelling venous catheter.

The subject sat in a contour chair placed behind the pedals of a cycle ergometer so that during exercise his legs were parallel to the floor. After instrumentation and establishment of thermal equilibrium, 15 minutes of resting data were collected. Thirty minutes of exercise at ~58% peak aerobic power¹ immediately followed the rest period. All thermoregulatory variables were measured twice each minute.

Data were analyzed by a three way analysis of variance (drug by activity by environment) and are presented as the mean and the standard

¹The peak aerobic power was measured in the week prior to the first day of testing during incremental exercise in this seated position. The oxygen uptake peak was determined as that point where no further change in oxygen uptake occurred following an increase in the ergometer resistance.

deviation.

Results

The oral administration of pyridostigmine bromide decreased the activity of red blood cell cholinesterase by 39 (± 7)% ($p < 0.05$). The red blood cell cholinesterase activity averaged $11.8 (\pm 0.7) \mu\text{mol} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}$ before PYR treatment and was reduced to $7.2 (\pm 1.0) \mu\text{mol} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}$ 150 minutes after treatment. SkBF was lower at rest in PYR by 40% at 29°C and by 30% at 36°C ($p < 0.05$). FBF was unchanged at rest, which indirectly shows increased muscle blood flow, as skin blood flow was lower. The mean thermoregulatory variables measured at rest for the three environments are given in Table 1 for both CON and PYR. Resting esophageal temperature (T_{es}) was not different in any of the six experiments. Mean skin temperature was different in each environment, by design, but was not affected by PYR at rest. There was significant bradycardia at rest in the PYR experiments compared to CON at both 29°C and 36°C ($p < 0.05$).

During exercise at 29°C and 36°C , SkBF was decreased by 40 and 50% by PYR, respectively (Table 2). Data for a single subject during all six experiments are shown in Figure 1; and show the change in SkBF between CON and PYR experiments. Furthermore, the differences in SkBF at the three distinct skin temperatures are also evident. FBF was not different during exercise between CON and PYR in any environment, which was indirect evidence of increased muscle blood flow. T_{es} was not different between PYR and CON during exercise at 22°C or 29°C (Table 2). However, T_{es} was higher at 36°C in PYR compared to CON ($p < 0.05$). T_{es} was higher at 36°C during exercise in both PYR and CON than the other two environments ($p < 0.05$). The change in esophageal temperature from rest to steady-state exercise was not

different between CON and PYR at 22°C (0.69°C vs 0.66°C) or 29°C (0.84°C vs 0.92°C). However, at 36°C the increase in T_{es} averaged 0.93° for CON and 1.06° for PYR ($p < 0.05$). Whole body sweating during exercise was higher only at 29°C. Forearm sweating during exercise was higher at 36°C in PYR compared to CON (Table 2).

The decrease in plasma volume calculated from hematocrit and hemoglobin values from rest and during cycle exercise averaged -9% in CON and -6% in PYR ($p = 0.22$).

Discussion

Skin blood flow decreased at rest and during exercise after the oral ingestion of pyridostigmine bromide. This decrease in skin blood flow or cutaneous perfusion decreased skin temperature subtly in the hottest environment (0.2°C) which precipitated the establishment of a less favorable temperature gradient for heat exchange between the skin and the environment, thus increasing heat storage. Decreased skin blood flow may have resulted from cholinergic stimulation centrally, at either pre- or postganglionic synapses, or directly at vasomotor elements. Pyridostigmine may have a direct effect as well. These sites and/or possible mechanisms of action cannot be addressed by the design or data of this study.

We tested the effect of both core and surface temperature on sweating and skin blood flow at three distinct ambient temperatures. In the coolest environment (22°C), the acute administration of the carbamate, pyridostigmine, did not affect heat production or dissipation. The effect or lack of an effect on temperature regulation at this ambient temperature was not surprising as the thermal gradient for dry heat loss was wide

enough to dissipate heat produced during exercise. Little evaporative cooling occurred as sweat secretion was low. At 29°C, decreased skin blood flow and bradycardia were observed at rest and during exercise. At this ambient temperature, heat transfer from the warmer skin to the cooler environment was sufficient to maintain core temperature. Skin and ambient temperature were closely matched at 36°C. In fact, heat was transferred from the environment to the skin. This condition necessitated the evaporation of secreted sweat to maintain body temperature. Pyridostigmine decreased skin blood flow, thus creating an even larger thermal gradient between the ambient air and the skin, thus heat storage increased compared to the control experiment.

In the present study, we were not able to consistently show significant differences in either local or whole body sweating, with the exception of whole body sweating at 29°C and forearm sweating at 36°C in PYR compared to CON. It appeared that the exercise period was not long enough to observe an increase in water loss via sweating and/or respiration in all test conditions, which is a likely effect of PYR administration.

Muscle blood flow as measured indirectly by changes in total limb blood flow increased in an inactive arm at both rest and during leg exercise after the administration of an anticholinesterase in this study. This was not unexpected as blood vessels in the muscle have cholinergic innervation (2,6,13,14). Increased muscle blood flow did not appear to have any adverse or beneficial effects during seated cycle exercise. However, in conditions where considerable venous pooling occurs, the observed increased muscle blood flow may have adverse consequences if

baroreflex activity is already affected by the accumulation of acetylcholine. This possibility should be investigated.

As far as can be determined by a review of the available literature (1,4,5,11), there are no studies done on human subjects which examine thermoregulatory consequences resulting from anticholinesterase therapy. Studies run on rodents (4,11) indicated that heat storage was increased and running time was compromised after acute pyridostigmine treatment in a 26°C environment (heat stress for this species). It was suggested that increased metabolic heat production resulted from excess sodium that leaked through cell membranes forcing increased sodium pump activity, thus increased heat storage (11). However, no change in dry heat dissipation has been reported in the rodent as measured tail skin temperature, which can be an indirect estimate of skin blood flow, was not different in pyridostigmine treated animals than control (11). Weight loss (urine, feces, saliva, respiratory water) per unit time ($\text{g}\cdot\text{min}^{-1}$) was higher after acute pyridostigmine treatment (11). However, the total weight loss (g) during the experiment was not different between control and pyridostigmine experiments as running time was shorter in pyridostigmine experiments (11). The thermoregulatory responses of the laboratory rat to acute carbamate treatment (4,11) are not representative of those responses seen under similar conditions in humans. Although heat storage was higher during thermal stress in rodents after PYR, the mechanism involved appeared different between the species. Vasomotor changes which can critically compromise heat exchange in humans were not observed in the rodent. The proposed increased heat production resulting from alterations in sodium pump activity was not observed at rest or during exercise in human

subjects.

The effect of sustained oral pyridostigmine therapy (5 daily 0.4 mg/kg doses) in an exercising primate (e. patas) has recently been reported (1). Animals treated with pyridostigmine significantly increased running time compared to control experiments, which appeared to be the result of decreased heat storage due to a 60% increase in whole body water loss. This increased water loss appeared to be from sweating, as panting has not been observed in this primate. Thus, core temperature remained lower during exercise resulting from increased evaporative heat loss. No measurement of dry heat loss was reported in these experiments (1).

Decreased skin blood flow affected heat exchange at 36°C as evidenced by the greater heat storage compared to CON. At 36°C, heat production was approximately 350 W·m⁻² and approximately 360 W·m⁻² was eliminated through evaporation during steady state exercise in control experiments. Thus, the small change in dry heat exchange (heat gain from the environment) after pyridostigmine ingestion, increased heat storage. If the water vapor pressure of the environment were higher, heat exchange via the evaporation of secreted sweat would be limited by the low water vapor pressure gradient between the skin surface and the ambient air. In this case, dry heat loss, the physical heat exchange by convection and radiation, becomes increasingly important to maintain the deep body temperature. Skin blood flow is the major determinant of dry heat loss. Therefore, in any condition at rest or during exercise in which heat exchange from skin blood flow is critical, temperature regulation will be affected during pyridostigmine treatment.

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Figure Legend

Figure 1. Cutaneous perfusion or skin blood flow measured by laser doppler velocimetry (LDF) in a single subject during CON and PYR experiments at the three environments tested. The open symbols are for control experiments at 22°C, 29°C and 36°C; the filled symbols are for pyridostigmine experiments at the same temperatures.

Table 1. Mean ($\pm$ SD) Thermoregulatory variables measured at rest for four subjects in CON and PYR experiments in three environments.

	Esophageal Temperature (°C)	Mean Skin Temperature (°C)	Cutaneous Perfusion (mV)	Forearm Blood Flow (ml·100ml ⁻¹ ·min ⁻¹)	Forearm Sweating (mg·cm ⁻² ·min ⁻¹)	Heart Rate (b·min ⁻¹)
CON 22°C	36.51 (0.10)	30.21 (0.55)	2 (1)	0.5 (0.2)	0.09 (0.03)	62 (9)
PYR 22°C	36.51 (0.15)	30.02 (0.75)	4 (3)	0.8 (0.4)	0.12 (0.09)	62 (9)
CON 29°C	36.38 (0.09)	33.43 (0.07)	25 (12)	2.3 (1.3)	0.13 (0.03)	66 (6)
PYR 29°C	36.41 (0.13)	33.40 (0.17)	15* (6)	2.3 (1.4)	0.19 (0.08)	58* (4)
CON 36°C	36.49 (0.16)	35.63 (0.31)	57 (9)	3.6 (1.7)	0.24 (0.11)	70 (9)
PYR 36°C	36.44 (0.12)	35.45 (0.43)	39* (16)	4.5 (2.5)	0.28 (0.15)	61* (6)

* Different from CON, $p < 0.05$.

Table 2. Mean ($\pm$ SD) Thermoregulatory variables measured during exercise for four subjects in CON and PYR experiments in three environments.

	Esophageal Temperature (°C)	Mean Skin Temperature (°C)	Cutaneous Perfusion (mV)	Forearm Blood Flow (ml·100ml ⁻¹ ·min ⁻¹)	Forearm Sweating (mg·cm ⁻² ·min ⁻¹)	Heart Rate (b·min ⁻¹)	Sweating Rate (g·min ⁻¹)
CON 22°C	37.20 (0.24)	31.11 (0.97)	42 (14)	5.6 (5.2)	0.56 (0.12)	132 (14)	8.0 (3.7)
PYR 22°C	37.18 (0.16)	30.54 (0.90)	41 (28)	4.3 (2.4)	0.47 (0.22)	128 (13)	9.2 (4.6)
CON 29°C	37.22 (0.27)	33.33 (0.77)	114 (19)	14.2 (3.9)	0.76 (0.29)	140 (14)	11.2 (4.1)
PYR 29°C	37.33 (0.24)	33.07 (0.57)	68* (31)	14.2 (4.1)	0.76 (0.14)	131* (14)	12.9 (3.9)
CON 36°C	37.41 (0.37)	35.47 (0.24)	143 (26)	11.9 (6.2)	1.03 (0.25)	163 (11)	17.8 (4.8)
PYR 36°C	37.50* (0.48)	35.26 (0.12)	72* (17)	18.3 (7.5)	1.36* (0.27)	145* (14)	15.7 (3.1)

* Different from CON, $p < 0.05$.

