AD-A129 717 PYRIDOSTIGMINE-INDUCED CHOLINESTERASE INHIBITION: EFFECTS ON THE ABILITY T..(U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA R FRANCESCONI ET AL. 1/1

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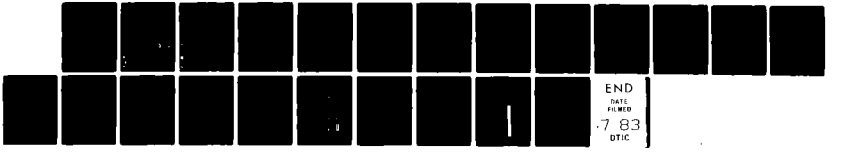

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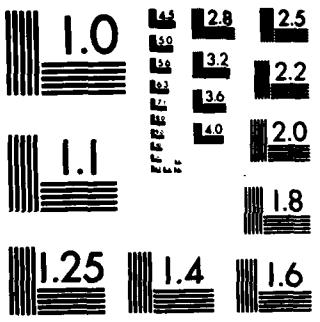

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER M26/83	2. GOVT ACCESSION NO. AD-A129717	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Pyridostigmine-induced cholinesterase inhibition: effects on the ability to work in the heat		5. TYPE OF REPORT & PERIOD COVERED 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Ralph Francesconi, Roger Hubbard and Milton Mager		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Research Institute of Environmental Medicine Natick,MA 01760		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 3A161101BS10 34382101005 BS10C Sys Hlth Haz Rsch
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research & Development Command Ft. Detrick, MD 21701		12. REPORT DATE 27 May 1983 13. NUMBER OF PAGES 13
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office) Same		15. SECURITY CLASS. (of this report) 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

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Same

18. SUPPLEMENTARY NOTES

NA

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

endurance, heat gain, hyperthermic exhaustion, pathochemical indices

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Adult, male rats (300-325 g) were treated with pyridostigmine bromide (n=22) or saline (n=22) to quantitate the effects of severe (64%) cholinesterase inhibition on the ability to work (9.14 m/min, level treadmill) in the heat (35°C). Pyridostigmine-treated rats had a mean endurance of 23 min while saline-treated animals ran for nearly 35 min ($p < .001$). Rates of rectal and skin temperature increments were significantly higher ($p < .001$) in pyridostigmine-treated rats as were water losses ($p < .001$). While exercise in the heat to hyperthermic exhaustion effected anticipated increments in circulating urea nitrogen, creatinine, lactate

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dehydrogenase, and potassium levels, pyridostigmine pretreatment had additive effects on lactate and creatine phosphokinase concentrations. Additionally, pyridostigmine effected a significant ($p<.01$) hyperglycemia prior to exercise. We concluded that pyridostigmine-induced cholinesterase inhibition had a variety of debilitating effects during work in the heat.

Pyridostigmine-induced cholinesterase inhibition: effects on the ability to work in the heat

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Running Title: Cholinesterase inhibition and work in the heat

Abstract

Adult, male rats (300-325 g) were treated with pyridostigmine bromide (n=22) or saline (n=22) to quantitate the effects of severe (64%) cholinesterase inhibition on the ability to work (9.14 m/min, level treadmill) in the heat (35°C). Pyridostigmine-treated rats had a mean endurance of 23 min while saline-treated animals ran for nearly 35 min ($p < .001$). Rates of rectal and skin temperature increments were significantly higher ($p < .001$) in pyridostigmine-treated rats as were water losses ($p < .001$). While exercise in the heat to hyperthermic exhaustion effected anticipated increments in circulating urea nitrogen, creatinine, lactate dehydrogenase, and potassium levels, pyridostigmine pretreatment had additive effects on lactate and creatine phosphokinase concentrations. Additionally, pyridostigmine effected a significant ($p < .01$) hyperglycemia prior to exercise. We concluded that pyridostigmine-induced cholinesterase inhibition had a variety of debilitating effects during work in the heat.

Key words: endurance, heat gain, hyperthermic exhaustion, pathochemical indices

Introduction

In continuing our studies on the identification and quantitation of factors which limit the ability to work in the heat (7-9) in an exercising rat model, we have recently reported (6) that moderate malathion-induced cholinesterase inhibition had no decremental effects on work tolerance. In the latter experiments plasma cholinesterase activity in rats was inhibited by 35% following consecutive daily dosages of malathion, yet physical, physiological, and thermoregulatory efficiency were unaffected. The impetus for this study came in part from the apparent paucity of information available regarding the effects of organophosphates on physical performance and thermoregulatory efficiency in animals during exercise in the heat. Behavioral and mental performance decrements as a result of organophosphate intoxication were well documented and reviewed (4), while several reports had noted the hypothermic effects of organophosphates in sedentary rodents in moderate environments (1,20).

The effects of cholinesterase inhibition on work performance and heat tolerance were also of extreme interest to us because atropine, an effective antidote to organophosphate toxicity (11,12), decreased heat tolerance (3,5) through its anti-cholinergic activity (2,16). We have recently demonstrated (14) that rats treated with atropine had a significantly increased rate of heat storage when subjected to a 41.5°C environment. This observation could be explained by the greatly decreased urine- and saliva-spreading behavior among the atropinized rats; both of these are important behavioral mechanisms of heat-dissipation in heat-stressed rats. However, no systematic studies have as yet been undertaken on the combined effects of agent-antidote treatment on the ability to work in a hot environment in an appropriate animal model (13,15). In the present investigation we are reporting the effects of severe cholinesterase inhibition, induced by carbamate pretreatment (11), on endurance, thermoregulation, and pathophysiology during exercise in a hot environment.

Methods

Adult, male rats (approx 300-325 g) were obtained from the Charles River Breeding Laboratories (Wilmington, MA) and housed singly in wire-bottomed cages at an environmental temperature of 21°C ± 1°C. Food (Ralston Purina Rodent Chow) and water were available ad lib, and an automatic timing device controlled fluorescent lighting (on, 0600-1800 h). Rats were held under these conditions for at least one week before experimentation to acclimate the animals to the ambient conditions and to entrain the normal diurnal/nocturnal periodicities of body temperature. Naive animals were used in all experiments since no adaptational effects of either heat or exercise stress were being considered. Ordinarily, untrained rats will readily run at the slow treadmill speed selected for these experiments.

A gift of pyridostigmine bromide (crystalline) was generously provided by Hoffman-LaRoche, Nutley, New Jersey. Samples (2-3 mg) of pyridostigmine were dissolved in appropriate quantities (100 µg pyridostigmine bromide/100 µl NaCl) of sterile non-pyrogenic saline solution. A number of preliminary experiments were performed to establish dose-response relationships and time sequencing for administration of the pyridostigmine bromide and appropriate inhibition of circulating cholinesterase activity. We concluded that the following dosage and timing sequence provided the targeted levels of inhibition without acute effects on thermoregulatory responses or locomotion. Rats were initially injected intraperitoneally with 300 µg pyridostigmine bromide, delivering 207.9 µg pyridostigmine. Exactly 60 min later 200 µg of pyridostigmine bromide (138.6 µg pyridostigmine) was adminstered, and 30 min later a final dosage (100 µg of the bromide salt, 69.3 µg of the free base) was administered. Following the final injection each animal was fitted with a rectal probe (model #701, Yellow Springs Inst. Co., Yellow Springs, OH) inserted 6 cm beyond the anal sphincter and a

surface probe (Yellow Springs #709) securely affixed midlength on the tail. During the ensuing 15 min the rats were restrained and rectal (T_{re}) and skin (T_{sk}) temperatures were monitored at 5 min intervals.

On the day prior to pyridostigmine administration each rat was fitted with an indwelling Silastic catheter (external jugular vein) for rapid and convenient blood sampling. The catheter was inserted under Nembutal^{R} (Sodium pentobarbital) anesthesia (50 mg/kg body weight) under aseptic conditions. This minor surgical procedure had no untoward effects on the subsequent ability to exercise in the heat. When this catheter was implanted, a small blood sample (0.8 ml) was obtained to establish normal or control levels of plasma cholinesterase activity as well as baseline levels of the clinical chemical indices of heat/exercise injury (9,13,15). Hematocrit levels were also measured, and the blood sample was centrifuged (10000 g, 4°C, 10 min), and the plasma removed and frozen (-20°C) for subsequent analysis.

At 13-15 min following the final (third) injection of pyridostigmine, a second blood sample (pre-run, 0.8 ml) was taken and treated identically as the first. This sample was necessary to quantitate the degree of cholinesterase inhibition effected by pyridostigmine and also to establish the effects, if any, of pyridostigmine adminstration on the clinical chemical indices of heat/exercise injury. In these experiments a group of carefully weight-matched control rats was treated identically save for the intraperitoneal injection of physiological saline equivolumetrically, but without pyridostigmine.

After the pre-run blood sample was withdrawn, the rat was quickly removed to a large (3 m x 4 m x 2m) stainless steel chamber maintained at 35°C $\pm$ 0.5°C (25%-30% RH). Each experimental and control rat was run (level treadmill, 9.14 m/min) to hyperthermic exhaustion (Tre $\tilde{=}$ 43°C, animal unable to right itself) at which time a third blood sample (post-run) was removed. While on

the treadmill T_{re} and T_{sk} temperatures were monitored on a minute-to-minute basis. Following removal of the postrun blood sample the rat was then returned to the holding room.

All plasma samples were assayed for the commonly reported indices of heat/exercise injury as well as cholinesterase activity. The latter was quantitated using kits purchased from Sigma Chem. Co. (St. Louis, MO) with slight modification (reduced volumes, continuous monitoring of optical density) of procedures noted in their technical bulletin (#420). Plasma glucose concentrations were established using Worthington Statzyme test kits while lactate was measured with kits purchased from Sigma; each assay was executed after procedures described in the respective technical bulletins. Potassium (K^+) and sodium (Na^+) were determined by flame photometry (Radiometer, Copenhagen). The remaining assays (creatine phosphokinase, lactic acid dehydrogenase, urea nitrogen, and creatinine) were performed using Worthington test kits by methods described in the appropriate technical bulletins. Most spectrophotometric procedures were carried out on a Gilford Stasar III semi-automated spectrophotometer; however, cholinesterase activity was measured using a Zeiss PM QII research spectrophotometer.

Statistical analyses were performed by the non-paired t test and by analysis of variance (19); the analysis of variance was followed by Tukey's t test for all-pair comparisons (18). The null hypothesis was rejected at $p < .05$.

Results

Fig. 1 demonstrates the effects of pyridostigmine administration and exercise in the heat to hyperthermic exhaustion on circulating levels of cholinesterase activity. The results indicate that administration of pyridostigmine prior to the experimental run resulted in a significant ($p < .01$)

decrement (64%) in cholinesterase activity. However, exercise in the heat to hyperthermic exhaustion had no effects on cholinesterase activity in either the pyridostigmine- or saline-treated rats.

Fig. 2 illustrates the effects of pyridostigmine treatment on the rectal temperature responses during exercise in the heat to hyperthermic exhaustion. The vertical arrows depict the mean time to hyperthermic exhaustion observed for both groups of animals. While control rats achieved a mean treadmill time of 34.7 $\pm$ 1.4 min ($\bar{X} \pm$ SEM), the corresponding endurance among pyridostigmine treated rats was only 23.1 $\pm$ .9 min ($p < .001$). Fig. 2 also demonstrates that in the pyridostigmine-treated rats the rates of rectal temperature increments were significantly ($p < .05$) greater, particularly between 10-23 min of treadmill time. Fig. 3 indicates similar response of T_{sk} to exercise in the heat. Fig. 4 demonstrates that during the treadmill run there occurred a significant ($p < .001$) increment in the average rate of weight (water) loss (.49 g/min vs .32 g/min) in the pyridostigmine-treated rats.

Table 1 summarizes the effects of pyridostigmine pretreatment and exercise in the heat to hyperthermic exhaustion on several clinical chemical indices of heat injury. It should be noted that pyridostigmine pretreatment effected a significantly ($p < .01$) increased level of circulating glucose in the pre-run sample (190 mg/100 ml vs 157 mg/100 ml, control) and in both groups exercise in the heat to hyperthermic exhaustion resulted in significant ($p < .01$) decrements. As anticipated, lactate levels were significantly ($p < .01$) increased in both groups in the post-run samples, but it is interesting to note that when the post-run samples are compared, pyridostigmine-treated rats displayed a significant ($p < .01$) increment. The statistically significant ($p < .01$) elevation pre-run to post-run in Na^+ levels in the pyridostigmine-treated rats is of questionable physiological importance since no statistical difference occurred

between the post-run samples of both groups. While exercise in the heat to hyperthermic exhaustion resulted in significantly ($p < .01$) increased levels of potassium, urea nitrogen, creatinine, and lactate dehydrogenase, pyridostigmine pretreatment had no effects on these indices. Alternatively, whereas creatine phosphokinase activity was not significantly affected in control animals by this short duration run, a significant ($p < .01$) increase was noted in the post-run samples of the pyridostigmine-treated rats.

Discussion

The results of the present investigation indicate that strong (64%) inhibition of circulating cholinesterase activity resulted in significantly reduced endurance capacity, compromised thermoregulatory efficiency, and exacerbated effects on several pathochemical indices of heat/exercise injury in the rat. This is in direct contrast to our earlier work (6) with malathion wherein moderate (35%) cholinesterase inhibition had relatively minor effects on physiological responses. While a variety of investigations have examined the effects of organophosphate-induced cholinesterase inhibition on mental performance (4,17), physiological responses (21,25), and metabolism (22,24), very little has been reported relative to the effects of carbamate-induced cholinesterase inhibition.

The results of the present study demonstrate conclusively that after pyridostigmine pretreatment hyperthermic exhaustion is reached in an abbreviated time interval when rats are exercised in a hot environment. These data indicate that their endurance is severely attenuated by the apparently severe effects of pyridostigmine pretreatment on heat gain, heat storage, and dehydration during the exercise interval. For example, quantitative examination of several indices of thermoregulatory efficiency demonstrated that pyridostigmine-treated rats gained heat (ΔT_{re} /min) at a significantly ($p < .001$)

increased rate while on the treadmill. Furthermore, it is also important to note that during the treadmill interval pyridostigmine-treated animals lost water (.49 vs .32 g/min) again at a greatly ($p < .001$) increased rate. It appears reasonable to conclude that the increased cholinergic activity resulting from cholinesterase inhibiton effected a greatly increased rate of salivary secretion (14,23) in the hot environment. While saliva-spreading would ordinarily be a useful mechanism of behavioral heat-loss in heat-stressed rats, it appears that the exercise contingency prevented the efficient utilization of the excessive salivary secretion for heat dissipation. Consequently, increased heating rates, despite incremented water loss, contributed to the rapid attainment of body temperatures incompatible with continued exercise peformance.

It is worthwhile to consider also the effects of pyridostigmine pretreatment on several of the pathochemical indices of heat/exercise injury. Initially, it should be noted that in the pre-run blood samples pyridostigmine administration effected a significant circulatory hyperglycemia. While such a hyperglycemia had been noted previously (22) in organophosphate-treated animals, this effect of pyridostigmine had been heretofore unreported. While Ramu and Korner (22) postulated that accumulation of acetylcholine centrally could partially explain this hyperglycemic effect, we cannot at this time rule out the possibility of pyridostigmine-induced catecholamine or glucocorticoid secretion, in turn effecting increased glycolysis or gluconeogenesis.

There also occurred several instances wherein pyridostigmine pretreatment exacerbated the incremental effects of heat/exercise injury on several circulating pathochemical indices. Thus, postrun levels of lactate and creatine phosphokinase were significantly ($p < .01$) elevated in pyridostigmine-treated rats when compared to saline-treated controls. There had been reported previously several instances of the additive or synergistic effects of

organophosphate administration and stressful stimuli on biochemical responses of experimental animals. For example, Gupta and Kapoor (10) demonstrated that irradiation prior to malathion administration produced additive effects on the activity of alkaline and acid phosphatases and succinic dehydrogenase in rat liver and spleen. Villeneuve et al. (25) demonstrated increased inhibition of plasma cholinesterase and plasma and liver carboxylesterase activities when food restriction was coupled with dietary parathion. Yamada et al. (26) compared the effects of organophosphates and carbamates on guinea pig ileum, and concluded that the carbamates may induce contraction by their anti-cholinesterase activity as well as a direct effect on smooth muscle. However, the effects of neither organophosphates nor carbamates on the indices of heat/exercise exhaustion have been documented. The results of the present study indicate a direct effect of pyridostigmine on exercising muscle since the excessive circulating lactate and creatine phosphokinase probably originate in these muscles. This hypothesis is strengthened by the observation that creatine phosphokinase levels are not altered in the saline-treated rats; such an observation is not unexpected given the mild exercise intensity and short duration of the present experiments.

We concluded from these experiments that intense cholinesterase inhibition, induced by pyridostigmine administration, severely limited the endurance capacity of rats working in the heat. Hyperthermic exhaustion was attained more quickly in these animals partially as a result of apparent thermoregulatory decrements. Further, effects of pyridostigmine pretreatment and exercise in the heat to hyperthermic exhaustion on several clinical chemical indices of heat/exercise injury indicate a direct effect of pyridostigmine on exercising muscle.

Acknowledgements

The authors gratefully acknowledge the skilled technical assistance of Gregory Smith, Virginia Pease and Natalie Leva. We also thank Sandra Beach, Pat Basinger and Julie Cyphers for typing the manuscript.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official US Department of the Army position, policy, or decision unless so designated by other official documentation.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resource National Research Council.

Figure Legend

Fig. 1. Effects of pyridostigmine bromide administration and exercise (9.14 m/min) in the heat (35°C) to hyperthermic exhaustion ($T_{re} \tilde{=} 43°C$) on plasma levels of cholinesterase activity. Pyridostigmine-treated rats (n = 22) received 207.9 µg pyridostigmine, followed in 1 h by 138.6 µg and again in 30 min by 69.3 ug; control rats (n = 22) received equivalent volumes of sterile non-pyrogenic saline. The blood samples (0.8 ml) were removed at the time of catheterization, immediately before exercise (pre-run), and immediately after exercise (post-run).

Fig. 2. Effects of pyridostigmine pretreatment on rectal temperature during exercise in the heat to hyperthermic exhaustion. All conditions are as noted under Fig. 1.

Fig. 3. Effects of pyridostigmine pretreatment on skin temperature during exercise in the heat to hyperthermic exhaustion. All conditons are as noted under Fig. 1.

Fig. 4. Effects of pyridostigmine pretreatment on the rate of weight (water) loss during exercise in the heat to hyperthermic exhaustion. All conditions are as noted under Fig. 1.

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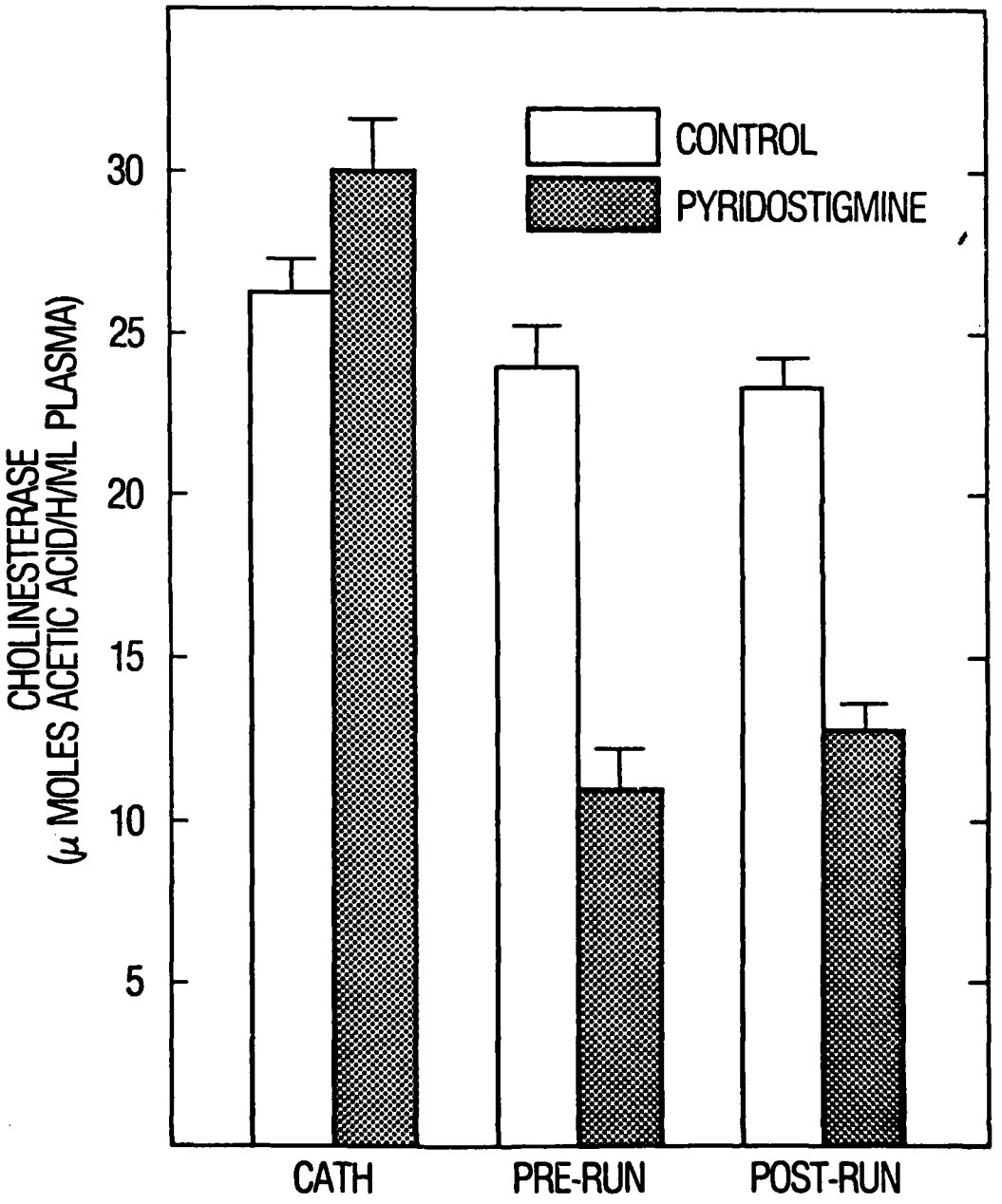
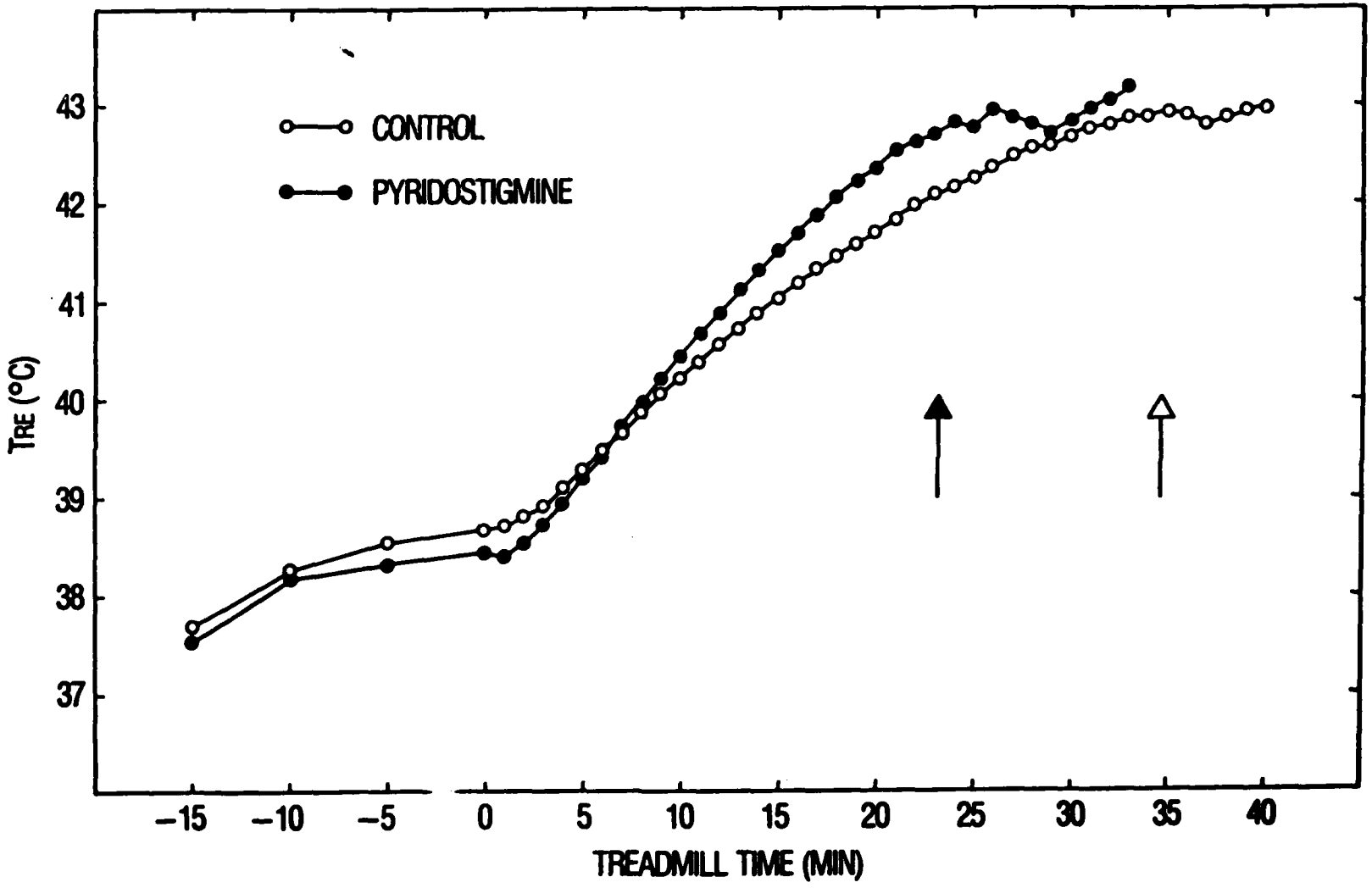

CONTROL
PYRIDOSTIGMINE
CHOLINESTERASE
(μ MOLES ACETIC ACID/H/ML PLASMA)
30
25
20
15
10
5
CATH
PRE-RUN
POST-RUN

Fig 1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PYRIDOSTIGMINE
TRE (°C)
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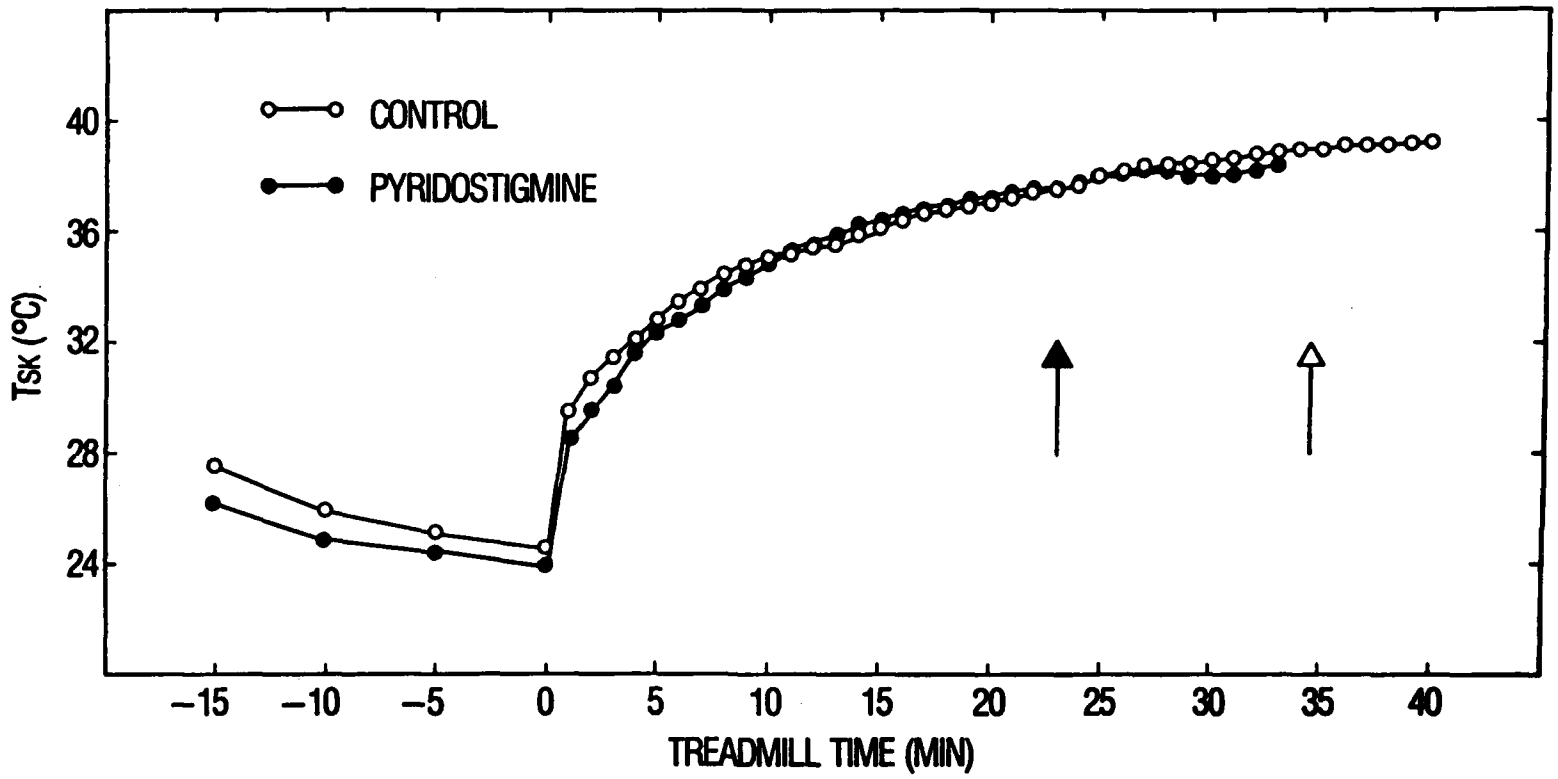
TREADMILL TIME (MIN)

Fig 2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28
24
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TREADMILL TIME (MIN)

Fig 3

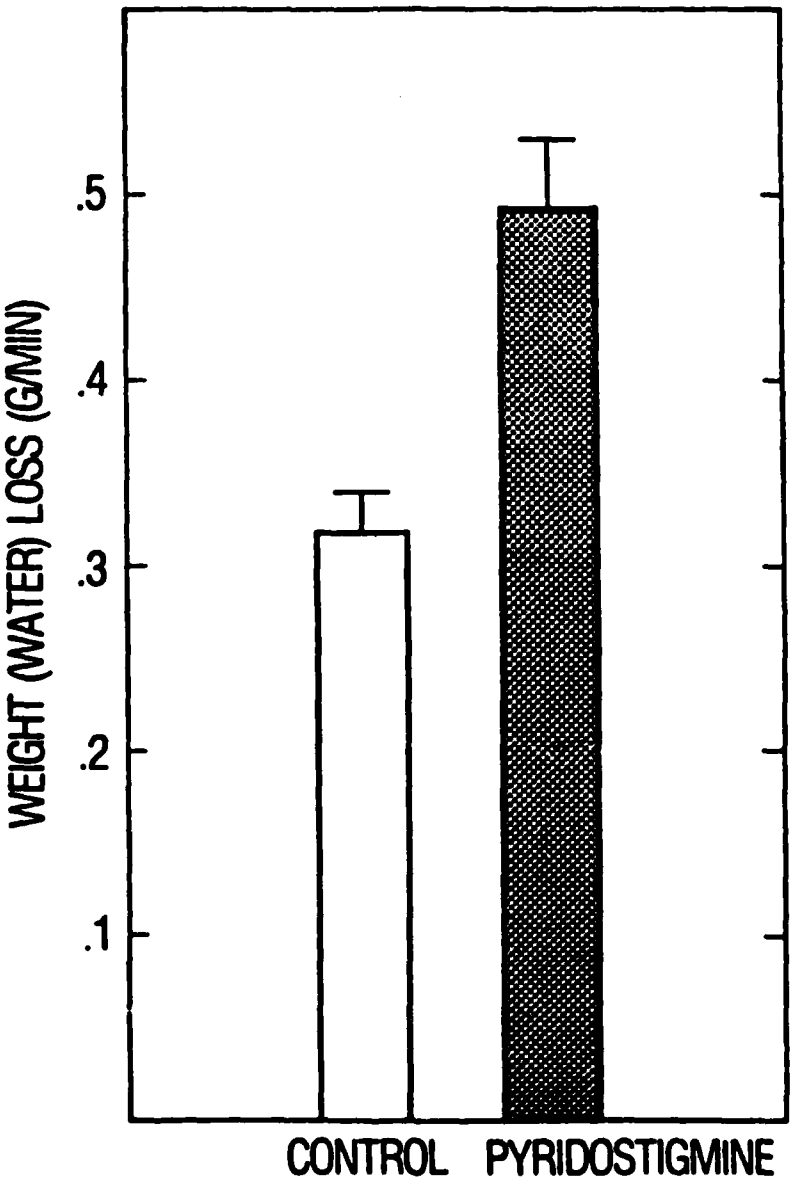

Fig 4

EFFECTS OF PYRIDOSTIGMINE PRETREATMENT AND EXERCISE IN THE HEAT TO HYPERTHERMIC EXHAUSTION ON PLASMA INDICES OF HEAT/EXERCISE INJURY

	CONTROL			PYRIDOSTIGMINE		
	CATH*	PRE-RUN	POST-RUN	CATH	PRE-RUN	POST-RUN
GLUCOSE (MG/100 ML)	169.05 ± 4.33	157.41 ± 3.08	120.36 ± 7.67	171.50 ± 3.67	189.82 ± 5.41	132.14 ± 9.35
LACTATE (MG/100 ML)	22.45 ± .98	12.98 ± 1.25	66.43 ± 7.01	21.49 ± 1.15	13.20 ± 1.36	105.51 ± 8.11
SODIUM (MEQ/L)	141.36 ± .58	142.82 ± .76	143.82 ± .60	140.41 ± .67	141.14 ± .81	145.50 ± .78
POTASSIUM (MEQ/L)	3.95 ± .08	4.58 ± .10	6.51 ± .18	4.10 ± .07	4.36 ± .09	6.81 ± .24
UREA NITROGEN (MG/100 ML)	15.72 ± .43	15.34 ± .48	22.07 ± .96	15.32 ± .58	16.89 ± .65	21.91 ± .68
CREATININE (MG/100 ML)	.60 ± .02	.64 ± .02	1.35 ± .04	.61 ± .02	.68 ± .02	1.28 ± .03
LACTATE DEHYDROGENASE (U/L)	69.15 ± 7.33	111.53 ±20.86	374.24 ±73.78	87.16 ±10.97	140.65 ±13.83	423.28 ±46.84
CREATINE PHOSPHOKINASE (U/L)	259.55 ±32.96	107.55 ± 9.41	196.69 ±48.22	200.65 ±11.96	248.15 ±24.24	510.17 ±55.98

MEAN VALUES ± STANDARD ERROR OF THE MEANS ARE NOTED FOR AN N = 22 IN BOTH GROUPS

*SAMPLE TAKEN AT THE TIME OF CATHETERIZATION

Table 1