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Title Aprophren and Scopolamine: Metabolic and Clinical Chemical Effects During Exercise

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APROPHEN AND SCOPOLAMINE: METABOLIC AND CLINICAL CHEMICAL EFFECTS DURING EXERCISE

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ABSTRACT

Adult, male rats (425 g) were pretreated with intravenously administered saline (C, Control, 200 ul), low dosage scopolamine (LS, 18.1 ug/kg), high dosage scopolomine (HS, 35.6 ug/kg), low dosage aprophren (LA, 3.6 mg/kg), or high dosage aprophen (HA, 6.3 mg/kg) 15 min prior to exercise (11 m/min, 6° incline) in a warm (26°C) environment. A small blood sample (0.8 ml) was removed from a permanently implanted jugular catheter immediately prior to drug administration and subsequent to completion of exercise (99 min or inability to continue). HS signnificantly ($p<0.01$) reduced endurance capacity (56.9 min, HS vs 87.8 min, C) and increased heating rate (0.053°C/min, HS vs 0.032°C/min, C). While endurance was slightly attenuated in HA (73.1min) and heating rate was minimally increased (0.038°C/min), the effects on neither variable achieved statistical significance. While circulating sodium levels in all groups were generally unaffected by pharmacological intervention or exercise ($p>0.05$), the mean plasma potassium concentration of HS-treated rats was significantly ($p<0.01$) greater post-exercise than comparable levels in LS, LA, and HA-treated animals. Despite the reduced endurance capacity of the HS group, this was the only treatment group that manifested a significant ($p<0.01$) pre to post exercise elevation in circulating lactate levels. These results indicated that of the drugs and doses evaluated, only the high dosage scopolamine had marked effects on several circulating indices of heat/exercise injury as well as performance. Significant elevations in post-exercise plasma lactate levels in this group indicate that HS may be having a metabolic effect impacting upon heating rate and physical performance.

INTRODUCTION

While not as extensively studied or widely used as atropine, both scopolamine and aprophen are potentially effective anticholinergic therapies for the variety of pathological effects of the anticholinesterases (6,7). However, as with atropine, both anticholinergics are not without significant deleterious effects on performance, both mental and physical, as well as thermoregulation (1,2,12). In fact, in a recent report we have compared the increments in core temperature of sedentary heat-stressed rats following administration of various drugs to quantitate their relative anticholinergic potencies (9). We had previously reported (10) that heating rate is one of the most sensitive indices of anticholinergic activity in rats. We concluded that scopolamine was the most efficacious of the compounds tested and manifested a relative potency of 16 in comparison to an equimolar dosage of atropine for the variables examined; however, we did not assess the effects of aprophen in this earlier paper. Thus, the current study was designed to evaluate the effects of two doses of scopolamine or aprophen on physical performance, thermoregulation, and clinical chemical responses during exercise in a warm environment.

MATERIALS AND METHODS

Adult male Sprague-Dawley rats were purchased from the Charles River Breeding Laboratories (Wilmington, MA) at approximately 350-400 g, and maintained in windowless rooms (22^{o}C) for at least 1 week prior to experimentation. Food (Purina Rat Chow) and water were available ad lib except during the actual experimental trials; animals were housed singly in wire-bottomed cages, and a 12 hour light/dark cycle (on, 0600-1800 h) entrained diurnal/nocturnal periodicities. Rats (n = 12/group) ordinarily weighed between 400-450 g at the time of the experiment.

Two days before an experimental trial each animal was fitted with a permanent indwelling catheter in the external jugular vein for drug administration and rapid and convenient blood sampling. A small blood sample (0.8 ml) was removed approximately 20 min before a treadmill bout and immediately upon termination of the treadmill run for analysis of several indices of heat/exercise injury. Rats were then weighed and at approximately 15 min before initiation of the run, 200 ul of sterile physiological saline (Control) or one of the drug dosages in 200 ul saline was administered IV to each animal. Animals in the low-dosage scopolamine group received 18.1 $\pm$ 0.33 ug/kg (X + SEM) while the high-dosage group received 35.6 $\pm$ 0.54 ug/kg. The dosages for the comparable aprophen groups were 3.57 + 0.04 and 6.28 + 0.09 mg/kg, respectively. Current doctrine calls for the use of the single dosage therapy irrespective of body size; thus, the slight variability was induced by the small differences in body size of the experimental animals. Rats were exercised on a motor-driven treadmill (26^{o}C, 11 m/min, 6^{o} angle of incline) by a shock-avoidance contingency. Rectal and skin temperatures were automatically acquired at 1.5 min intervals and the treadmill bout continued for 99 min or when the rat reached hyperthermic exhaustion (Tre = 41 - 42^{o}C, animal unable to right itself). A second (post-run) blood sample was taken, instrumentation was removed, a post-run weight was determined, and the animal was returned to its home cage. Blood samples were centrifuged (16000 x g), and a small aliquot of the plasma was immediately assesed for osmolality. The remainder of the plasma fraction was quickly frozen, stored (-20^{o}C), and later analyzed for lactate (Gilford semi-automated spectrophotometer), and sodium and potassium (Radiometer, Copenhagen, Flame Photometer). Statistical analyses were performed by analysis of variance followed by the application of Tukey's test to determine the critical differences of the means necessary for statistical significance. The null hypothesis was rejected at $p<0.05$.

RESULTS

Fig. 1 demonstrates the effects of the pharmacological interventions on endurance capacity. Under these conditions control animals ran for 87.8 $\pm$ 4 min, and while low-dose scopolamine had no effects on endurance, high dose scopolamine significantly ($p<0.01$) reduced endurance (56.9 min). The data indicate that while aprophen had no significant effects on physical performance in the doses administered, high-dosage aprophen attenuated mean run time (73.1 + 7.5 min). Fig. 2 illustrates that the reduction in endurance displayed in the high-dosage scopolamine-treated rats arose at least in part due to an increased rate of rise of core temperature in this group. At 60 min run time the mean temperature of the high dosage scopolamine group is approximately 1^{o}C higher than that of each of

FIG. 1

EFFECTS OF TWO DOSES OF SCOPOLAMINE (18.1 AND 35.6 μG/KG) AND APROPHEN (3.6 AND 6.3 MG/KG) ON ENDURANCE (11 M/MIN) AT 26°C.

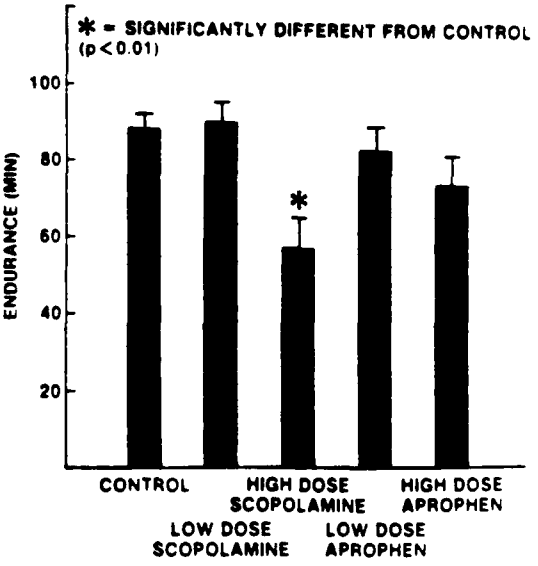

FIG. 2

EFFECTS OF TWO DOSES OF SCOPOLAMINE AND APROPHEN ON THE CORE TEMPERATURE RESPONSE TO EXERCISE AT 26°C.

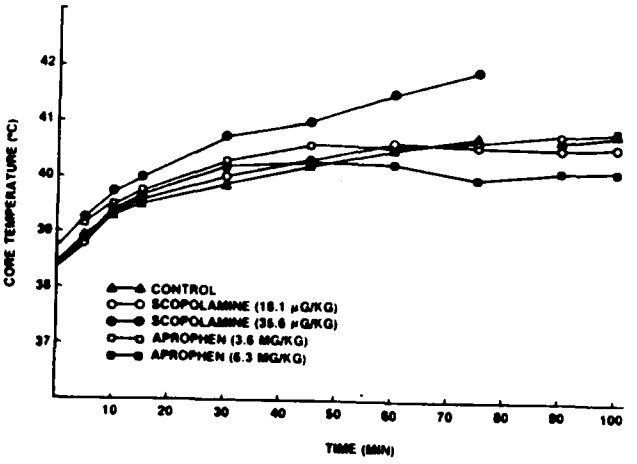

TABLE 1

EFFECTS OF TWO DOSES OF SCOPOLAMINE AND APROPHEN AND EXERCISE AT 26°C ON CIRLULATING LEVELS OF SODIUM, POTASSIUM, AND LACTATE

	CONTROL	SCOPOLAMINE (18.1 μG/KG)	SCOPOLAMINE (35.6 μG/KG)	APROPHEN (3.6 MG/KG)	APROPHEN (6.3 MG/KG)
	PRE POST	PRE POST	PRE POST	PRE POST	PRE POST
SODIUM (MEQ/L)	142.2 143.8 ±0.9 ±0.7	143.9 145.5 ±.6 ±0.6	142.7 145.3 ±0.9 ±1.1	143.0 145.3 ±0.7 ±1.0	143.4 144.3 ±0.8 ±1.7
POTASSIUM (MEQ/L)	4.86 4.80 ±0.3 ±0.2	4.78 4.29 ±0.1 ±0.3	4.85 5.44 ±0.1 ±0.2	4.86 4.44 ±0.1 ±0.1	4.58 4.42 ±0.1 ±0.2
LACTATE (MG/DL)	18.7 43.9 ±4.4 ±7.9	16.8 30.4 ±2.3 ±8.4	19.8 61.3* ±3.1 ±10.8	20.0 31.0 ±3.4 ±6.3	20.4 28.0 ±4.1 ±5.1

* - SIGNIFICANTLY DIFFERENT FROM PRE p<0.01

the other groups. The apparent decrement in core temperature of the high-dosage aprophen group at 75 min actually arises due to termination of the run by several animals with moderately high core temperature between 60 and 75 min. Neither potassium nor sodium (Table 1, $p>0.05$) levels were affected by either the pharmacological intervention or the mild exercise in the warm environment. However, data on circulating lactate levels (Table 1) demonstrated an apparent metabolic effect of the high-dosage scopolamine. In this group pre- to post-exercise levels (19.8 to 61.3 mg/dl) of lactate were significantly different ($p<0.01$) while the moderate increments in all other groups failed to achieve statistical significance; thus, the combination of exercise in a warm environment and high-dosage scopolamine elicited a significant elevation in circulating lactate levels.

DISCUSSION

In our early studies (8,10) we used dosages of atropine ranging from 5 - 1000 ug/kg to evaluate the effects of this anticholinergic on heating rate in a sedentary, heat-stressed rat model. Freireich et al. (5) had earlier hypothesized that an equivalent drug dose for a rat should be on the order of 7-fold greater than the dosage of the same drug for a human on a per kilogram basis. Since our experimental work with rats indicated that a standard dose of 200 ug/kg atropine elicited optimal anticholinergic properties, we used this particular dosage extensively in some of our subsequent work (10,11). When we compared the anticholinergic potency of a variety of drugs to this standardized dosage of atropine, we found in our passive heating experiments that scopolamine had a potency ratio of approximately 16 in comparison to atropine (9). Thus, in the current experiments we evaluated the effects of approximately 1.4 and 2.8 times the equivalent standardized dosage (200 ug/kg) of atropine in rats. Likewise, we selected dosages of aprophen that were up to 2.1 times the equivalent

atropine dosage to assure eliciting pharmacological effects of aprophen in our model of human heat/exercise injury. The results of these experiments indicate that the high-dosage scopolamine had the more severe effects as judged by endurance capacity, heating rate, and apparent metabolic effects.

It is clear from Fig. 1 that the high-dosage scopolamine-treated rats manifested markedly compromised endurance capacity, partially accounted for by a significantly increased heating rate. In fact, the mean heating rate (increase in Tre/min while on the treadmill) for this group (0.053°C/min) was significantly higher than that of all other groups (Control = 0.032°C/min, $p<0.01$, Low Scopolamine = 0.029°C/min, $p<0.01$, Low Aprophen = 0.031°C/min, $p<0.01$, and High Aprophen = 0.038°C/min, $p<0.05$).

In some of our earlier work we used a warmer (35°C) environmental temperature in which to exercise the animals, and, subsequent to exercise in the heat, we observed far more prominent effects on several indices of heat/exercise injury and dehydration. For example, circulating levels of sodium, potassium, lactate, and osmolality (3,4), even in control animals, were notably increased in the earlier studies when compared to results of the present experiments. In these previous studies it is noteworthy that both pyridostigmine and chlorpromazine treatment resulted in increased lactate concentrations subsequent to exercise despite decreased performance times. In the current experiments also the high dosage of scopolamine elicited a significantly ($p<0.01$) increased lactate concentration (Table 1) subsequent to exercise despite the fact that the mean endurance among these animals was significantly less than that of any other group. This may indicate that the scopolamine pretreatment, in addition to exerting anti-muscarinic effects manifested in reduced salivary secretion rates, may be having notable nicotinic effects demonstrable in the increased post-run lactate levels in this group.

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