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Temperature-Dependent Effects of α-Adrenergic Agonists and Antagonists in the Cold

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CARLISLE, H. J. AND M. J. STOCK. *Temperature-dependent effects of α-adrenergic agonists and antagonists in the cold.* PHARMACOL BIOCHEM BEHAV 51(2/3) 263-270, 1995.—This series of experiments examined whether temperature-dependent effects of the α-antagonists prazosin and yohimbine compromised their use as blockers of α-adrenergic agonist responses in cold-exposed rats. An operant leverpressing task was used to measure the demand for heat in a cold environment. The α_1-antagonist prazosin had modest effects, but the α_2-antagonist yohimbine was thermolytic in that it dose dependently increased operant responding but decreased posttest colonic temperature (Tc). These potent effects of the α_2-antagonist led to tests of the α_2-agonist clonidine. Clonidine increased operant responding for heat to an extraordinary degree, resulting in significant increases in posttest Tc. However, clonidine was found to be a hypothermic agent when tested in rats at 5°C but denied the opportunity to increase body temperature by operant lever pressing, suggesting a central effect on the control of thermal balance. Measurement of changes in metabolic rate at 5 and 23°C showed that yohimbine increased metabolism at 23°C but decreased it in the cold. Prazosin had little effect on metabolism or Tc at either temperature. Prazosin inhibited the decrease in Tc induced by norepinephrine (NE), but had little effect on the lever-pressing response. Yohimbine had no significant antagonistic effect on NE-induced changes in lever-pressing behavior or posttest Tc, but neither did the thermolytic effects of yohimbine exacerbate those of NE. These results show that α-antagonist interactions with agonists can be complicated by temperature-dependent effects of each.

Prazosin Yohimbine Clonidine Norepinephrine Temperature regulation Behavior Rat

THE SYMPATHETIC nervous system is of paramount importance in the regulation of many diverse aspects of energy and thermal balance (3,17,28). The adrenergic agonists norepinephrine (NE), epinephrine (EPI), and isoproterenol (ISO) are all thermogenic when tested at a thermoneutral ambient temperature (Ta) but, unexpectedly, disrupt thermal balance (i.e., have thermolytic effects) in the cold (6,7,39). The basis for the paradoxical effects of NE and EPI is not clear, but those of ISO can be attributed to β_2-adrenoceptor activation because the selective β_2-antagonist ICI 118551 completely reverses these effects (8,10). The β_2-mediated mechanism producing thermolytic effects in the cold, presumably vasodilatation (9), could also be the basis for the paradoxical effects of NE and EPI, but the evidence thus far suggests an α-adrenoceptor involvement. Yohimbine, an α_2-antagonist, was more effective than propranolol (nonselective β-antagonist) in reversing the decrease in metabolic rate induced by NE in a cold Ta, but it did not influence the NE-induced fall in body temperature (40). The reason for the discrepancy between the effects of yohimbine on metabolic rate and body temperature is not clear. The mixed α-antagonist phentolamine blocks the paradoxical effects of EPI in the cold at a dose of 100 μg/kg, but this effect diminishes as the dose of phentolamine increases (6).

One hypothesis regarding these ambiguous results is that α-antagonists have temperature-dependent effects alone, and these complicate the interpretation of results when agonist-antagonist interactions are studied. For example, phentolamine results in a decrease in colonic temperature (Tc) attributable to a decrease in metabolic rate in the cold and to vasodilatation at a neutral Ta (24). The hypothermic effects are dose and temperature dependent (19). Consistent with these effects, phentolamine increases operant responding for convective

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warming in a cold Ta (31). In a study of both behavioral and autonomic thermoregulatory responses to phentolamine, Kent and Satinoff (18) found hypothermic effects that depended on the responses available and the Ta. Phentolamine increased heat loss at both 2 and at 22°C. Metabolic rate increased in the cold, but not until body temperature decreased; similarly, operant responding for convective warming occurred, but only after body temperature decreased. This work is consistent with a thermolytic effect of phentolamine when the dose is on the order of 5–10 mg/kg.

The selective α_1-antagonist prazosin has antipyretic effects (34,35), and it blocks the increase in metabolism induced by cold exposure (13). Prazosin alone would therefore be expected to have thermolytic effects in the cold. The selective α_2-antagonist yohimbine is thermogenic at a neutral Ta (14), and its lipolytic and other metabolic effects (20,29) suggest no reason why it should not remain thermogenic in the cold.

The purpose of the present study was to examine the effects of prazosin and yohimbine on thermoregulatory behavior and thermal balance in a cold environment to determine whether the use of these antagonists might help explain the ambiguous results when they are used as blocking agents against various agonists. Yohimbine was found to be thermolytic in the cold, and this led to tests of the α_2-agonist clonidine to determine its effects on thermal balance. The effects on metabolic rates of selected doses of these drugs were tested at a neutral and cold Ta; the selective antagonists were tested against NE in the lever-pressing task in a cold Ta.

METHOD

Animals

Thirty female Sprague–Dawley rats were obtained from Charles River Laboratories when they were 3 mo of age. The animals were maintained individually in hanging wire cages and fed Purina Chow (5001) and water ad lib. The colony room was maintained at 22°C with a relative humidity of 50%, and a 12 L : 12 D cycle (lights on 0700 h); all tests were conducted during the light phase of the cycle.

Drugs

(−)-Norepinephrine bitartrate was obtained from Winthrop Pharmaceuticals (New York City, NY). The α_1-antagonist prazosin HCl, α_2-antagonist yohimbine HCl, and α_2-agonist clonidine HCl were obtained from Sigma (St. Louis, MO). All drugs except prazosin were dissolved in normal saline (0.9% NaCl), which also served as the control vehicle. Prazosin was dissolved in a 25% propylene glycol (PG) solution at a concentration of 1 mg/ml; saline was used for dilutions of this stock solution. The PG vehicle was tested alone as the control for prazosin doses. Dosage for the various drugs (specified subsequently) was based on previous work (13,14,18,21,40).

Lever-Press Apparatus

The test apparatus allowed animals to obtain unlimited heat in a cold environment by pressing a lever to activate infrared heat lamps. A circular wire-mesh cage 22 cm in diameter and 22 cm deep was equipped with a 3 × 4 cm Plexiglas lever that protruded 5 cm into the cage 2 cm above the floor. Two 250-W red-bulb infrared lamps were mounted at each side of the cage at a 45° angle to the floor and focused on the rat at the lever. The power dissipated by the lamps was set to 300 W, which produced an irradiance of 180 mW/cm^2 as measured by an Eppley thermopile. The apparatus was placed in a 0.48-m^3 freezer maintained at −8 ± 2°C. A 25-W red incandescent lamp provided low-level background illumination. The heat lamps were activated by pressing the lever and remained on as long as the lever was held down. Equipment in an adjoining room provided a cumulative record of the pattern of responding as well as the number of lever presses and the cumulative duration of heat lamp activation.

Lever-Press Procedure

The animals were shaved closely with an Oster clipper the day before a test. The reason for shaving the animals was to prevent the sporadic performance that occurs as a result of piloerection when the fur is intact. The rats were trained to press the lever to activate the heat lamps, and then given at least four additional trials 90 min in duration so that operant responding for heat and body temperature were stable for two consecutive tests. The standard test procedure was to allow 30 min of baseline responding to permit adaptation to the test conditions, and to obtain a measure of Tc maintained by the behavior in the absence of drug treatment. The animal was removed from the test apparatus after the 30-min baseline, and Tc was measured with a Physitemp (Clifton, NJ) BAT-12 meter and thermocouple probe inserted 7 cm. The drug(s) for that test was then injected, and the animal returned to the apparatus for an additional 60 min. Tc was again measured on removal from the test. The animals were tested twice per week with 3–4 days intervening between tests.

Metabolic Measurements

The test chamber was a 6-l spherical chamber through which air was drawn at the rate of approximately 2l/min. We dried the effluent air by passing it through a column of Drierite (Ca2SO4), and an aliquot sample of 150 ml/min was routed to a Beckman Instruments (Fullerton, CA) OM-11 oxygen analyzer. This sample was then combined with the air that bypassed the analyzer for the measurement of total airflow with an American Singer dry gas meter. The voltage output of the oxygen analyzer was displayed on a Leeds & Northrup millivolt potentiometer for analysis of the amount of oxygen removed from the air at 2.5-min intervals over the course of the test. Oxygen consumption (ml O_2/min) was calculated from the average of these 2.5-min intervals, corrected to standard temperature and pressure (STP: barometric pressure of 760 mm Hg, 0°C), and converted to watts by multiplying by 0.337 (the product of the respiratory equivalent of 20.21 J/ml O_2 for a mixed diet and the conversion factor 1 W = 0.01667 J/min).

Metabolic Procedure

A baseline period of 30 min was given to permit adaptation to the test chamber and environmental conditions. The animal was then removed, the Tc was measured, and the drug for that test injected. The animal was then returned to the chamber for an additional 60-min test period, after which Tc was again measured. The data were analyzed for overall metabolic rate during the 60-min postinjection, and for the first and second 30-min intervals postinjection.

Protocols

Experiment 1 examined the effects of prazosin, yohimbine, and clonidine in the lever-press apparatus at a Ta of −8°C. Twelve rats each were assigned to prazosin and yohimbine

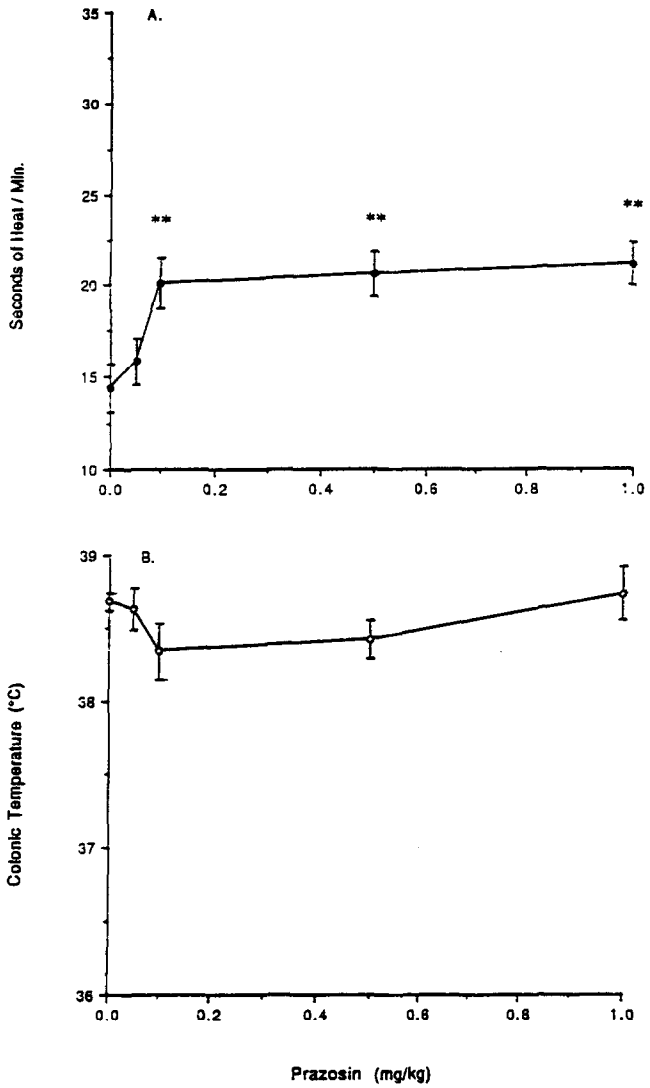

FIG. 1. The effect of prazosin doses on: (A) operant responding for heat and (B) posttest colonic temperature (Tc). $^{**}p < 0.01$ compared to vehicle alone (paired t-test).

groups. The doses of prazosin were 0.0 (prazosin vehicle PG alone), 0.05, 0.1, 0.5, and 1.0 mg/kg given intraperitoneally (IP). Yohimbine doses were 0.0 (saline), 0.5, 1.0, 2.5, and 5.0 mg/kg given IP. Body weight [(BW) ± SEM] of the prazosin group was 321 ± 9.7 g, and that of the yohimbine group, 336 ± 10.1 g. At the completion of the prazosin and yohimbine tests, six animals from each group were assigned to a clonidine group (BW = 344 ± 7.7 g), and the remainder were assigned to Experiment 3. Clonidine was administered IP in doses of 0 (saline), 5, 10, 15, and 25 μg/kg. The order of administration of the doses was counterbalanced within each drug group.

Experiment 2 examined the effect of selected doses of drugs on the metabolic rate of six female rats (BW = 323 ± 7.6 g) at a neutral Ta of 23°C and at a cold Ta of 5°C. One week intervened between the 23°C test and the 5°C test; these were given in counterbalanced order. Saline, prazosin (0.5 mg/kg IP), and yohimbine (1 mg/kg IP) were tested together in a counterbalanced order. Clonidine (0.1 mg/kg IP) was tested next, followed by NE alone [250 μg/kg given subcutaneously (sc)].

Experiment 3 examined the manner in which yohimbine and prazosin interacted with NE in the lever-press apparatus at a Ta of −8°C. Ten female rats (BW = 322 ± 8.2 g) from Experiment 1 were tested as described earlier. Each received saline, NE at a standard dose of 250 μg/kg (SC), and the NE dose plus prazosin or yohimbine in doses of 0.25 and 0.5 mg/kg (IP). Each animal received each treatment, which was given in a counterbalanced order.

Data Analysis

The primary data are the duration of heat lamp activation and the change in Tc resulting from the treatments. To evaluate how these variables interacted using common units, we calculated several derived measures of thermal balance, as described previously (7). The change in heat storage (dS, kJ) is the product of the change in Tc (posttest − preinjection), body mass, and the specific heat of the body (assumed to be 3.47 J/g). Heat influx (HI, kJ) is the amount of energy ab-

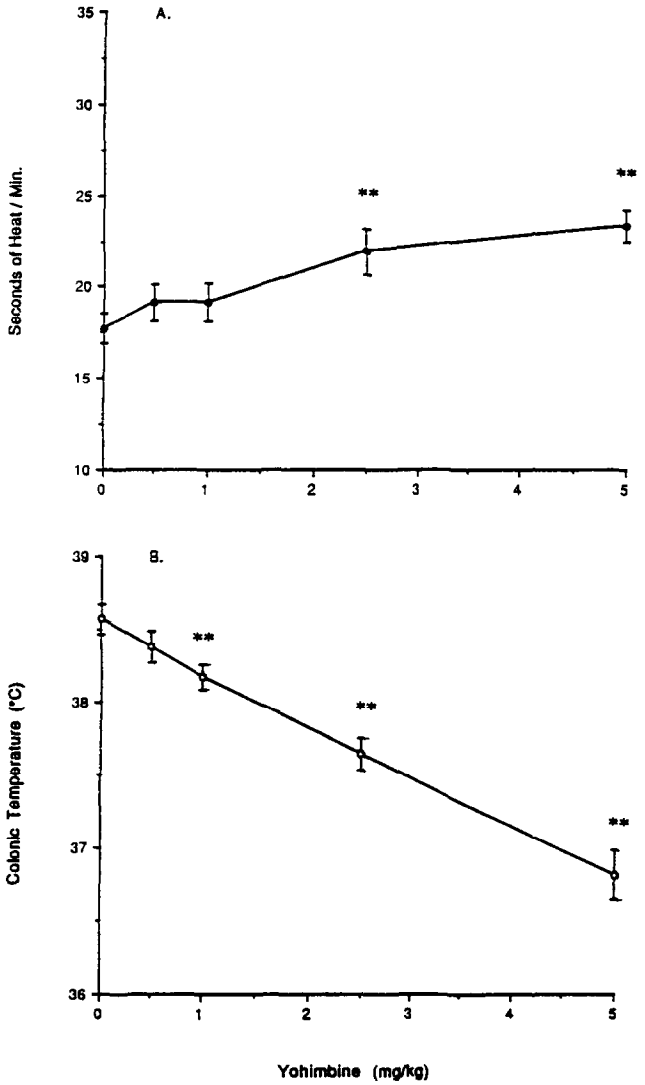

FIG. 2. The effect of yohimbine doses on: (A) operant responding for heat and (B) posttest Tc. $^{**}p < 0.01$ compared to saline (paired t-test).

sorbed from the heat lamps. HI considers primarily the surface area of the animal exposed to the radiant energy, and the irradiance and duration of activation of the lamps. Net heat loss (NHL, kJ) is the amount of energy absorbed less the change in heat stored (HI − dS). Because the amount of heat obtained (s/heat per min) could be influenced either by the duration of a response (s/heat per R) or the frequency of responding (R/min), these parameters were examined for consistent trends.

Analyses of variance were used to evaluate the overall effect of the drug treatments on the main variables of posttest Tc and the duration of heat lamp activation. Paired *t*-tests were used for specific comparisons either to saline or agonist alone. All probabilities are two-tailed.

RESULTS

Experiment 1

Figures 1-3 show the results for prazosin, yohimbine, and clonidine, respectively. These figures are plotted on the same scale to permit comparison of the relative magnitudes of the drug effects. Prazosin produced unusual dose-response effects, as shown in Fig. 1. Operant thermoregulatory behavior increased at very low doses of 0.05 and 0.1 mg/kg, but higher doses produced only a slight additional increment in behavior. Similarly, posttest Tc was affected more at low than high doses, but none of these changes was significantly different from saline. Preinjection Tc averaged 38.7°C for these tests. The thermal balance data shown in Table 1 reflect minimal effects on dS because of the small changes in posttest Tc, but significant increases in HI and NHL at doses of ≥ 0.1 mg/kg. Thus, prazosin increases heat-seeking behavior with modest effects on posttest Tc. The increase in operant behavior noted in Fig. 1 was accounted for by an increase in the frequency of responding. Response rate increased systematically from 1.3 R/min (0 dose) to 1.9 R/min at the 1-mg/kg dose (a 47% increase), whereas response duration varied little from the 11.2 s/R noted for the control dose.

Yohimbine produced a significant increase in operant behavior, as shown in Fig. 2, whereas posttest Tc decreased substantially and dose dependently as the yohimbine dose increased. The preinjection value of Tc was 38.7°C, averaged across doses. The thermal balance data in Table 2 show that HI increased systematically as the dose increased, but this increase did not compensate for heat loss and Tc fell resulting in a dose-dependent negative effect on dS. These effects added to produce substantial increases in NHL as a function of dose. Yohimbine is therefore thermolytic. The increase in operant behavior noted in Fig. 2 was due to an increase in the frequency of responding for doses of ≤ 2.5 mg/kg. Thus, frequency increased from 1.7 R/min after saline to 2.3 R/min at

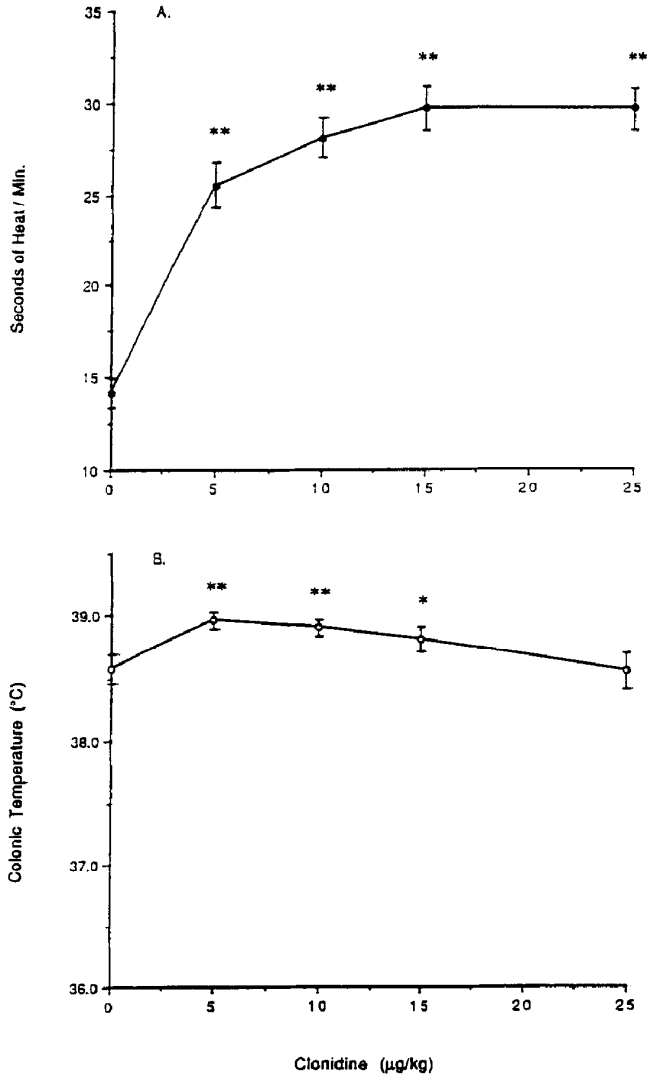

FIG. 3. The effect of clonidine doses on: (A) operant responding for heat and (B) posttest Tc. *$p < 0.05$; **$p < 0.01$ compared to saline (paired *t*-test).

TABLE 1

EFFECT OF PRAZOSIN ON THERMAL BALANCE

Dose (mg/kg)	dS (kJ)	HI (kJ)	NHL (kJ)
0.0	0.1 ± 0.11	18.6 ± 1.78	18.5 ± 1.74
0.05	−0.2 ± 0.18	19.9 ± 1.60	20.1 ± 1.64
0.1	−0.4 ± 0.13*	25.4 ± 1.84*	25.8 ± 1.87*
0.5	−0.1 ± 0.16	26.0 ± 1.78*	26.1 ± 1.88*
1.0	−0.1 ± 0.51	26.8 ± 1.79*	27.0 ± 1.86*

Values are means ± SEM ($n = 12$). dS, Change in heat storage; HI, heat influx; NHL, net heat loss.
*$p < 0.01$ compared to saline (paired *t*-test).

TABLE 2

EFFECT OF YOHIMBINE ON THERMAL BALANCE

Dose (mg/kg)	dS (kJ)	HI (kJ)	NHL (kJ)
0.0	−0.1 ± 0.11	23.6 ± 1.46	23.7 ± 1.45
0.5	−0.5 ± 0.10*	25.2 ± 1.52	25.7 ± 1.50
1.0	−0.6 ± 0.15*	25.5 ± 1.68	26.0 ± 1.66*
2.5	−1.3 ± 0.12†	29.1 ± 2.03†	30.4 ± 2.05†
5.0	−2.3 ± 0.20†	31.1 ± 1.55†	33.4 ± 1.64†

Values are means ± SEM ($n = 12$). Abbreviations as in Table 1.
*$p < 0.05$; †$p < 0.01$ compared to saline (paired *t*-test).

TABLE 3
EFFECT OF CLONIDINE ON THERMAL BALANCE

Dose (μg/kg)	dS (kJ)	HI (kJ)	NHL (kJ)
0	0.01 ± 0.12	18.4 ± 1.11	18.3 ± 1.05
5	0.3 ± 0.09*	33.2 ± 1.75†	32.8 ± 1.76†
10	0.4 ± 0.14†	36.6 ± 1.60†	36.3 ± 1.59†
15	0.2 ± 0.09	38.9 ± 1.86†	38.7 ± 1.88†
25	−0.03 ± 0.12	38.4 ± 1.63†	38.5 ± 1.67†

Values are means ± SEM (n = 12). Abbreviations as in Table 1.
*$p < 0.05$; †$p < 0.01$ compared to saline (paired t-test).

the 2.5-mg/kg dose (an increase of 34%) with little effect on response duration. At the 5-mg/kg dose, the frequency was 2.2 R/min, and response duration also increased from 10.2 s/R (saline) to 10.8 s/R (a 27%) increase.

Clonidine produced a remarkable increase (100% above control levels) in operant responding for heat, as shown in Fig. 3. This increase in responding resulted in significant increases in posttest Tc at doses of 5–15 μg/kg. Preinjection Tc averaged 38.6°C for these tests. The thermal balance data in Table 3 show a significant storage of heat at the lower doses, whereas HI increased substantially as a result of the increase in operant behavior. The rate of responding for heat remained significantly elevated at the higher doses, although the increment was not in proportion to the dose of clonidine. Posttest Tc decreased at the high doses with respect to the lower doses but not significantly with respect to saline. The increase in operant behavior seen in Fig. 3 was due to an increase in both the frequency of responding and the duration of a response. Thus, frequency increased from 1.5 R/min (saline) to an average of 2.3 R/min for the three high doses (an increase of 53%), whereas duration increased from 9.2 s/R (saline) to an average for the three high doses of 12.9 s/R (a 40% increase).

Experiment 2

Table 4 shows the results for metabolic rate measurements at a neutral Ta of 23° and a cold Ta of 5°C after the various drug treatments. Prazosin had no significant effect on metabolic rate or posttest Tc at either Ta. Yohimbine increased metabolic rate significantly at 23°C, and decreased it significantly at 5°C with no effect on posttest Tc at either Ta. Clonidine reduced metabolic rate and Tc at 23 and 5°C very substantially, but this was a high (100-μg/kg) dose compared to the highest dose tested (25 μg/kg) in the previous experiment. NE reduced metabolic rate as well as posttest Tc significantly in the cold. At 23°C, NE increased metabolic rate and decreased posttest Tc, but neither change was significantly different from saline.

Experiment 3

Figure 4 shows how prazosin and yohimbine interact with NE to influence thermoregulatory behavior and posttest Tc. The comparisons in this figure are with respect to NE alone. Thus, saline and NE differed significantly from each other, but no other treatment resulted in a significant effect with respect to NE for operant responding. For posttest Tc, saline and NE differed significantly from each other, and pretreatment with prazosin resulted in a significant increase in Tc with respect to NE. The increase in posttest Tc was greater for the lower dose of prazosin even though the increment in operant responding was less. Yohimbine had no significant effect on operant responding or posttest Tc with respect to NE, but posttest Tc was reduced significantly ($p < 0.05$) for the NE plus yohimbine dose of 0.5 mg/kg with respect to saline. The thermal balance data in Table 5 reflect these outcomes in that dS was improved significantly for both prazosin pretreatments with respect to NE, but HI increased as a result of the increase in operant responding, and neither HI nor NHL showed significant improvement with respect to NE alone. Yohimbine had no significant effect on any parameter with respect to NE alone. NE alone produced the increase in operant behavior seen in Fig. 4 by increasing both the frequency and duration of responding. Thus, frequency increased from 1.7 (saline) to 2.0 R/min (an 18% increase), whereas duration increased from 7.8 (saline) to 9.8 s/R (a 26% increase). Prazosin plus NE had no effect on frequency, whereas duration increased from 7.8 s/R (saline) to an average of 11.0 s/R for both doses (an increase of 41%). Conversely, yohimbine plus NE had no effect on duration, whereas frequency increased from 1.7 R/min (saline) to an average of 2.1 R/min for both doses (an increase of 18%).

DISCUSSION

The pharmacologic agents used in this study produced some unexpected results, but the effects of yohimbine and clonidine were the most surprising. There is not an extensive literature on the thermal effects of yohimbine, but thermo-

TABLE 4
EFFECTS ON METABOLIC RATE AND POSTTEST Tc AT A Ta OF 5°C AND 23°C

	5°C		23°C	
Treatment	MR (W/kg)	Tc-post (°C)	MR (W/kg)	Tc-post (°C)
Saline	14.4 ± 0.56	38.5 ± 0.14	8.1 ± 0.42	37.6 ± 0.35
Prazosin 0.5	13.7 ± 1.64	38.5 ± 0.21	7.8 ± 0.37	37.4 ± 0.19
Yohimbine 1.0	13.1 ± 0.27*	38.2 ± 0.19	9.3 ± 0.28*	37.5 ± 0.20
Clonidine 0.1	10.2 ± 0.70†	35.9 ± 0.58†	5.8 ± 0.14†	36.1 ± 0.18*
NE 0.25	10.7 ± 0.26†	36.6 ± 0.50†	9.4 ± 0.37	36.9 ± 0.30

All doses are milligrams per kilogram. Values are means ± SEM (n = 6). MR, Metabolic rate.
*$p < 0.05$; †$p < 0.01$ compared to saline (paired t-test).

genic effects were anticipated based on the ability of the drug to increase metabolism in a neutral Ta (14), its stimulatory effect on the sympathetic nervous system (20), and its lipolytic and other metabolic effects (20,29). Indeed, yohimbine produced a significant increase in metabolic rate at a Ta of 23°C in Experiment 2, but a decrease in metabolism at 5°C. In the operant thermoregulatory task, yohimbine produced unequivocal thermolytic effects. Despite the significant increase in operant responding for heat, posttest Tc decreased substantially and dose dependently as the yohimbine dose increased. This outcome indicates that yohimbine is seriously compromised as a useful antagonist for blocking adrenergic agonists in tests conducted in a cold Ta. What was perhaps more surprising was that yohimbine did not modify thermal balance when it was coadministered with NE. Because both NE and yohimbine separately produce an increase in lever pressing and a decrease in posttest Tc in the cold, it might be anticipated that both together would yield an exaggerated thermolytic effect. However, the effects of NE and yohimbine were clearly not additive, as shown in Experiment 3. Yohimbine can antagonize either pre- or postsynaptic α_2 adrenoceptors, although it has a preferential affinity for the presynaptic autoreceptor (33). Blocking this receptor provokes an outflow of NE (33), whereas whole-animal administration of yohimbine results in a significant increase in plasma NE (14). Thus, the failure of yohimbine to interact with NE may have been the result of very high levels of NE resulting from endogenous release as well as exogenous administration. It was noted previously (40) that yohimbine ameliorated the decrease in metabolic rate induced by NE in the cold without influencing the fall in Tc. This observation suggests that yohimbine may influence other (i.e., vascular) responses in the cold, perhaps via a presynaptic mechanism, resulting in a net thermolytic effect.

TABLE 5

EFFECT OF PRAZOSIN AND YOHIMBINE ON NE THERMAL BALANCE

Treatment	dS (kJ)	HI (kJ)	NHL (kJ)
Saline	0.1 ± 0.10	16.5 ± 1.72	16.4 ± 1.72
Norepinephrine	−0.7 ± 0.26*	24.2 ± 1.93*	25.0 ± 2.10*
NE + Yo 0.25	−0.4 ± 0.13†	23.1 ± 1.38*	23.5 ± 1.43*
NE + Yo 0.50	−0.6 ± 0.14*	21.0 ± 1.77*	21.7 ± 1.83*
NE + Praz 0.25	0.1 ± 0.13‡	21.8 ± 1.98*	21.6 ± 2.04*
NE + Praz 0.50	−0.1 ± 0.11†‡	24.9 ± 1.84*	25.1 ± 1.81*

Norepinephrine (NE) dose is 250 μg/kg. Prazosin (Praz) and Yohimbine (Yo) doses are milligrams per kilogram. Values are means ± SEM (n = 10). Abbreviations as in Table 1.

*$p < 0.01$; †$p < 0.05$ compared to saline (paired t-test). ‡$p < 0.05$ compared to NE alone (paired t-test).

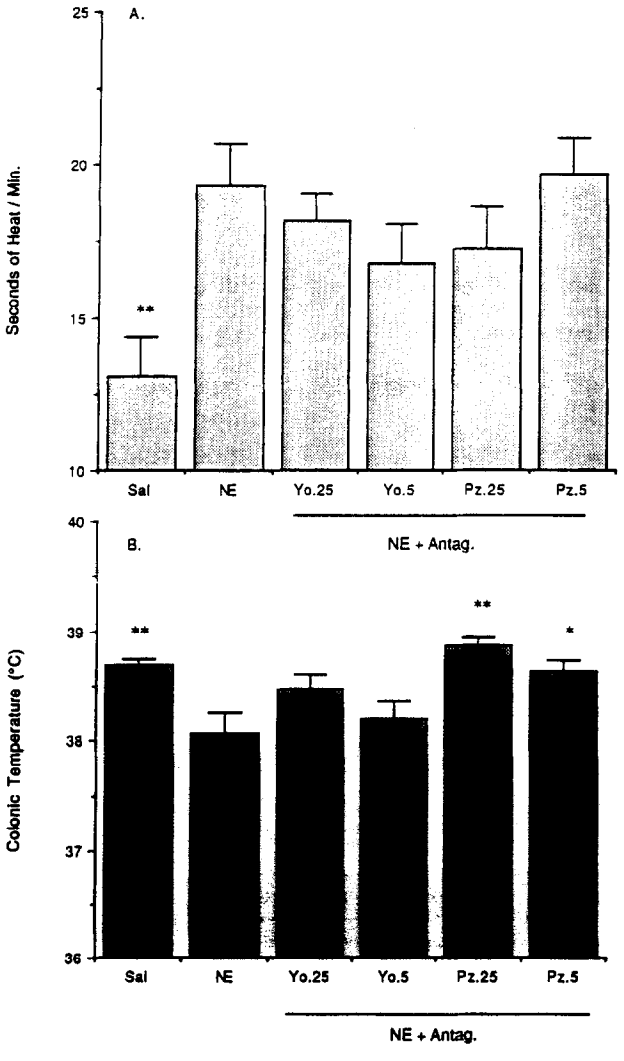

FIG. 4. The effect of norepinephrine (NE) alone (250 μg/kg) and with prazosin (Pz) or yohimbine (Yo) at doses of 0.25 and 0.5 mg/kg on: (A) operant responding for heat and (B) posttest Tc. Saline is shown for comparison. *$p < 0.05$; **$p < 0.01$ compared to NE alone (paired t-test).

Prazosin was expected to have thermolytic effects in the cold, based on its ability to block cold-induced as well as NE-induced thermogenesis (13). Prazosin failed to block the increase in metabolism induced by exposure to cold in Experiment 2 at a dose of 0.5 mg/kg. No effects of prazosin alone on metabolic rate or Tc were noted at 23 or 5°C in this experiment. When given alone, prazosin increased operant responding for heat significantly with little effect on Tc. Prazosin also ameliorated the posttest decrease in Tc induced by EPI in lean and obese Zucker rats (6). Because increased thermogenesis correlates with an increase in the density of BAT α_1 adrenoceptors (26), these effects of prazosin are probably not due to direct effects on thermogenesis. Both NE and EPI are vasoconstrictors in most vascular beds, but cold can induce constriction or dilation depending on the particular blood vessel and the distribution of α_1 and α_2 adrenoceptors in that tissue (11,12). The tail of the rat is a major avenue of heat loss in this species (27), and it contains both receptor subtypes with a predominance of α_1 (16). However, antagonism of this receptor by prazosin should result in increased rather than decreased heat loss as a result of vasodilation. Thus, the mechanism of the protective effect of prazosin on heat loss is uncertain.

Clonidine was expected to be a hypothermic agent because of reports of decreases in body temperature (21,36,38) and energy expenditure (32), as well as the sedative and antihypertensive effects of this drug. However, what was surprising about clonidine in this study was the significant increase in temperature produced by the extraordinary increase in operant responding for heat. The duration of heat lamp activation was greater for clonidine than for any other substance, including the catecholamines that have been tested recently (5-

10). The animals not only compensated for the thermolytic effects by working to maintain a Tc comparable to that seen after saline, but actively worked to increase Tc above normal.

The increase in operant responding and the rise in Tc suggest that clonidine is only hypothermic when the animal is deprived of behavioral control over its body temperature. In other words, clonidine causes hypothermia via its autonomic effects on heat production and heat loss, but alters thermoregulatory behavior (i.e., bar-press activity) such as to produce a mild hyperthermia. The behavioral response implies a central thermoregulatory effect, but the site of action of clonidine need not be at the same α_2 adrenoceptor antagonized by yohimbine. The eating response elicited by intrahypothalamic clonidine (2) has been attributed to stimulation of postsynaptic receptors because this response remains intact when catecholamines are depleted by α-methyl-*p*-tyrosine (15). Thus, the positive energy balance response of eating and the positive thermal balance responses noted here may reflect a common postsynaptic effect of clonidine. This hypothesis raises a question as to the endogenous ligand. NE is the most likely candidate, and some evidence shows that NE has hypothermic effects following intrahypothalamic injection (25,32), whereas other data indicate hyperthermic effects (1,30). These ambivalent responses to intrahypothalamic NE would be consistent with the ability of clonidine to produce divergent responses depending on the experimental conditions.

The divergent effects of clonidine on autonomic and behavioral responses bear some resemblance to the syndrome observed in the obese (ob/ob) mouse. This mutant exhibits impaired autonomic function, depressed sympathetic activity, hyperphagia, and chronic hypothermia (3,17). As in the present study with clonidine, the obese mouse readily demonstrates that the hypothermia is not a regulated phenomenon because the animal will work to raise body temperature to a normal level in an operant lever-pressing task (4). Perhaps the syndrome of effects noted in the ob/ob mouse reflects an overexpression of α_2 adrenoceptors resulting in responses comparable to those obtained by stimulation of α_2 adrenoceptors with clonidine in the normal animal. This suggestion may be too simple given the remarkable plasticity of brain α_2 adrenoceptors recently demonstrated by Levin and Hamm (22) and Levin and Planas (23) in animals either resistant or prone to develop obesity on a high-energy diet. Differences in both α_1 and α_2 adrenoceptors have been demonstrated in a number of brain areas of the resistant and prone animals (37), but the failure of the obesity-prone rats to modify α_2 receptors following glucose or diet manipulations (22,23) is a characteristic that defines this phenotype.

In conclusion, it would seem that the use of α-adrenergic agonists and antagonists to study thermoregulatory responses in the cold is clearly complicated by what appears to be dual, and often opposing actions on autonomic and behavioral mechanisms of thermal balance. Future experiments will have to be undertaken to see whether it is possible to separate these effects.

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