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Phentolamine and Thermoregulation in Rats

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KENT, S., M. HURD AND E. SATINOFF. *Phentolamine and thermoregulation in rats.* PHARMACOL BIOCHEM BEHAV **40**(4) 709–716, 1991.—Phentolamine (PHEN), a nonselective α-adrenoceptor antagonist, causes a dose and ambient temperature (Ta)-dependent fall in body temperature (Tb) when injected intraperitoneally. In this paper, we investigated whether this was caused by integrated behavioral and autonomic thermoregulatory responses and whether it was due to a central action of the drug. Male rats were trained to press a bar for warm air in the cold or cold air in the heat. Rats were tested in both conditions near their Tb peaks and troughs after injections of saline or PHEN (5 and 10 mg/kg, IP). Tb fell significantly within the first 30 min post-PHEN, and after that, in the cold, the rats worked to increase Ta. In the heat they did not change Ta. To determine what was responsible for the Tb fall, we measured heat loss and heat production after saline or PHEN (10 mg/kg; IP) at Ta 2, 20, and 30°C. Decreases in Tb at 2 and 20°C were caused by increased heat loss during the first 15–30 min post-PHEN. At 2°C, heat production increased after the drop in Tb. We conclude that the main reason the rats do not start to work immediately to prevent their core temperature from falling is that skin temperature is high, due to peripheral vasodilation, and that skin temperature is the major stimulus for regulating preferred Ta. We believe these effects are mediated by peripheral mechanisms because intracerebroventricular injections of PHEN did not cause a fall in Tb.

α-Adrenoceptor antagonist Behavioral thermoregulation Body temperature Heat loss Heat production Phentolamine Rat

ANY drug that changes body temperature (Tb) does so in one of two ways: 1) by activating a coordinated set of thermoregulatory reflexes and behavior designed to maintain thermal balance, (altering set-point) or 2) by modifying one or several thermoregulatory effector mechanisms. Either mode of action will alter the zone of thermal comfort, although in opposite directions (18). To attribute a change in Tb to an altered set-point, several conditions must be met. First, the same dose of a drug should produce similar changes in Tb at different ambient temperatures (Ta's), within the limits of the capabilities of heat loss and heat production systems. Second, all physiological and behavioral thermoregulatory responses should work in concert to produce the change in Tb. To alter Tb in the most efficient manner, different autonomic responses may be used at different Ta's. Third, the site of action for the change in set-point should be central, not peripheral.

Phentolamine (PHEN), a nonselective α-adrenoceptor antagonist, lowers Tb in a dose-dependent manner when injected intraperitoneally (IP) (5, 11, 12, 23). Because this effect also depends on the Ta (11–13) it would imply that PHEN is not acting to decrease a thermal set-point, but rather is acting on one or more thermoregulatory effectors. However, results in the literature are not consistent. After injecting PHEN IP, one group showed that rats behaviorally worked to increase Ta (19,20), which suggests that this drug is not acting via a change in setpoint. In contrast, another group concluded that the decrease in Tb post-PHEN was caused by coordinated reflexive thermoregulatory responses, which implies that set-point is lowered (13).

In the present paper we tried to reconcile these discrepancies. We first used operant thermoregulation to determine if the zone of thermal comfort was changed post-PHEN and if the Tb changes would be reinforced or counteracted behaviorally. We then measured autonomic heat loss and heat production at three Ta's, two below, and one at thermoneutrality. Finally, to determine if the mechanism of the hypothermia was central or peripheral, we measured Tb after intracerebroventricular (ICV) injections of PHEN. The results demonstrate that rats will work to counteract the drop in Tb after PHEN, that PHEN lowers Tb solely by an increase in heat loss produced by vasodilation and that it is not acting centrally.

GENERAL METHOD

All subjects were male hooded rats of the Long-Evans strain born and bred in the animal colony of the Psychology Department of the University of Illinois. They weighed 280–450 g at the start of the experiments. They were maintained from birth at Ta 23 ± 1°C on a 12:12 light:dark cycle in polycarbonate cages (45 × 23 × 18 cm). Food and water were available ad lib except during testing sessions.

The rats were anesthetized with an IP injection of a mixture of Ketaset (ketamine hydrochloride; 87 mg/kg) and Rompun (xylazine; 13 mg/kg), and then injected with atropine sulfate

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(0.54 mg/kg IP). A temperature telemetry device (1×2.1 cm cylinder, weight 2.3 g; Mini-mitter Co., Sunriver, OR) was implanted into the peritoneal cavity. The rats were then returned to their home cages for at least 1 week. Tb data were obtained through the implanted transmitter, which emits a broadband RF pulse at a rate proportional to its temperature. This signal was converted to a Tb value by a microcomputer.

EXPERIMENT 1: BEHAVIORAL THERMOREGULATION

In this experiment, the rats were given the opportunity to press a bar to alter the Ta. They were tested in both heat and cold at the time of their Tb peaks and troughs.

METHOD

General Procedure

Rats were trained to press a bar for warm air reinforcement in the cold (Ta 2±2°C; cold-escape) or cold air reinforcement in the heat (Ta 40±2°C; heat-escape). Training was as described in (21). During testing, the "reinforcement air" stayed on as long as the bar was depressed. Tb and Ta data were recorded every 5 s for 75 min before and 120 min after drug or vehicle injections. All injections were made 2–6 h after lights-on or lights-off.

Apparatus

The operant chamber was an insulated Plexiglas cylinder (19×41 cm) with a Plexiglas bar and grid floor. Hot (Ta 40±2°C) or cold (Ta 2±2°C) air was forced through a rotating valve, the position of which determined the temperature of the air reaching the chamber. Air flowed into the chamber through a baffled inlet located at the top, and was exhausted through an outlet under the grid floor. Chamber Ta was monitored by a thermistor under the floor near the outlet.

Drug Injections and Testing Schedule

Six rats were injected with PHEN HCl (5 mg/kg) in 1 ml isotonic saline or an equivalent volume of saline, and six with PHEN (10 mg/kg) or saline, in each of 4 conditions: in the heat and in the cold, when their Tb's were near their daily peaks and daily troughs. Thus each rat was tested 8 times. The order of exposure to the different conditions and the injections were counterbalanced, with at least 2 days between saline and PHEN injections and at least 4 days between PHEN injections. Tb was recorded continuously every 10 min. For tests conducted in the dark, a red light was used for illumination.

To determine the efficacy of the behavior, 5 rats were placed in the chamber without access to the bar (N=3 given 10 mg/kg; N=2 given 5 mg/kg). Two Ta's were used: 1) Ta 2°C for 70 min; 2) Ta 40°C for 45 min.

Data Collection and Analysis

Tb and Ta values were computer collected, recorded, displayed, and stored at 5 s intervals. Number of bar presses and the length of time the bar was depressed were also recorded. All data were analyzed in 15 min blocks, using a within-subjects 4-way ANOVA. A 2 (doses: 5 and 10 mg/kg) × 2 (treatments: saline and PHEN) × 2 (time of day: Tb peaks and troughs) design was used with repeated measures on the four (Ta) or five (Tb) pre- and eight postinjection 15 min blocks. Because the variances were dissimilar, separate analyses were conducted for the 2 conditions of heat- and cold-escape. In addition, separate analyses were conducted on the pre- and postinjection time periods. Planned comparisons were conducted at each block to determine significant differences between saline and PHEN.

RESULTS

Overall Summary

In general, PHEN caused a drop in Tb within 15–45 min. The largest changes were in the cold-escape condition at 10 mg/kg. Decreases in Tb were much smaller in all other conditions. In 3 out of 4 cold-escape conditions, the rats increased barpressing for heat and significantly raised the Ta. In the heat-escape conditions, Tb dropped significantly after PHEN, but there were almost no differences between the Ta's maintained by the drug and control groups (Figs. 1–4).

Cold-Escape

Before injection, the rats maintained the Ta 3–4°C lower at their Tb peak than they did at the trough ($p<0.025$). Lower Tb's 30 min post-PHEN (10 mg/kg) were correlated with lower Ta's during the first 15 min ($r=.80$; $p<0.005$). Minimum Tb's were recorded when Ta's and barpress durations were maximal. For the next hour, the rats worked to increase Ta, attaining mean 15 min maxima of 32.2±0.9°C at the peak and 30.7±0.7°C at the trough (Fig. 1a–f). For Ta to rise this much (13° at night and 9°C during the day) the rats barpressed enough to raise the Ta to 43°C for short periods of time. Ta's this high were never seen after saline injections.

Notwithstanding the increased barpressing for heat, Tb only slowly returned to preinjection levels. By two h post-PHEN (10 mg/kg) at the Tb peak, Tb still had not returned to control levels. However, the Tb of rats placed at 2°C without access to the bar dropped over 0.8°C in less than 20 min after PHEN, and were 4.2±0.3°C (N=3) lower than controls 75 min postinjection.

After the first 15 min post-PHEN (5 mg/kg), the rats consistently barpressed to increase Ta for the next 60 min at their Tb peak. Mean Ta's reached a maximum of 27.5±1.3°C at the Tb peak and 27.6±1.1°C at the Tb trough within 45–60 min (Fig. 2a–f). Tb's were lower during this time ($p<0.05$). Ta's were always at least equal to and sometimes as much as 8°C higher than the level maintained by control rats ($p<0.025$). These effects were greater at the Tb peak. Tb dropped slightly (0.5±0.2° at night and 0.4±0.2°C during the day) in the first 30 min post-PHEN, but had returned to control levels by 75 min postinjection. Tb's of rats without access to the bar (N=2) were 2.7±0.3°C lower than controls 75 min postinjection.

Heat-Escape

After PHEN (10 mg/kg) at the Tb peak, rats worked to lower Ta by 2°C in the first 15 min, but this was not significantly different from control levels (Fig. 3a and c). In the next 15 min, Ta increased 3.1±2.1°C at the Tb peak and 3.7±2.6°C at the Tb trough (Fig. 3 d–f). Increases ranged from 2 to 14°C, with the largest increases seen in those rats that had let the Ta drop the most in the first 15 min. Tb did not change during the first 15 min when Ta was decreasing; instead it dropped during the next 15 min when Ta was increasing (Fig. 3b). Tb's increased slightly during the remaining 90 min, returning to within 0.3°C of preinjection Tb's. Ta varied little during the final 90 min. Lower Tb's 30 min post-PHEN were correlated with the decrease in Ta during the first 15 min ($r=.80$; $p<0.005$). Tb's

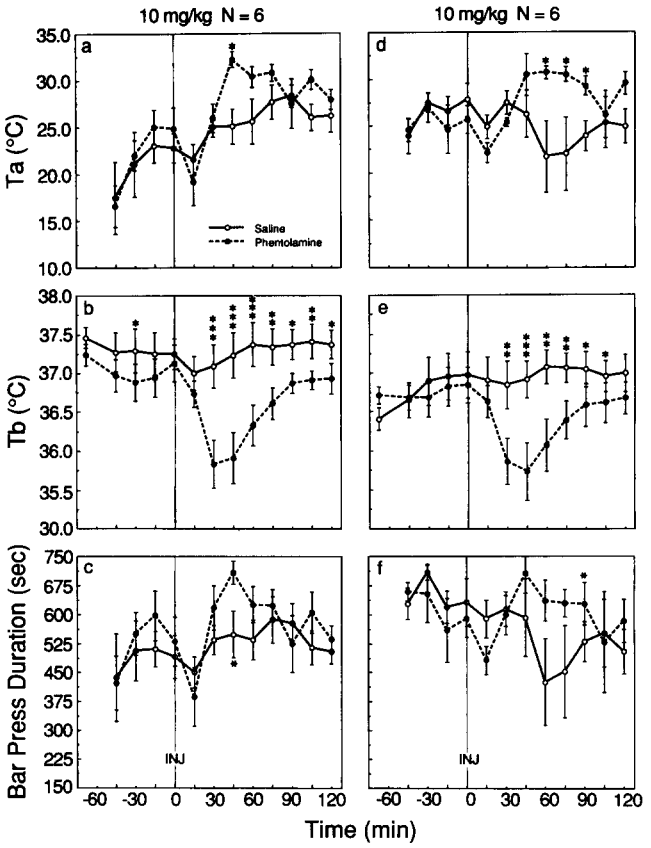

FIG. 1. Mean Ta, Tb, and length of time the bar was depressed for 60 min pre- and 120 min postinjection of PHEN (10 mg/kg) or saline near Tb peaks (left) and troughs (right) in the cold-escape tests. Each point is the average of the previous 15 min. *$p<0.05$; **$p<0.01$; ***$p<0.001$. N = 6.

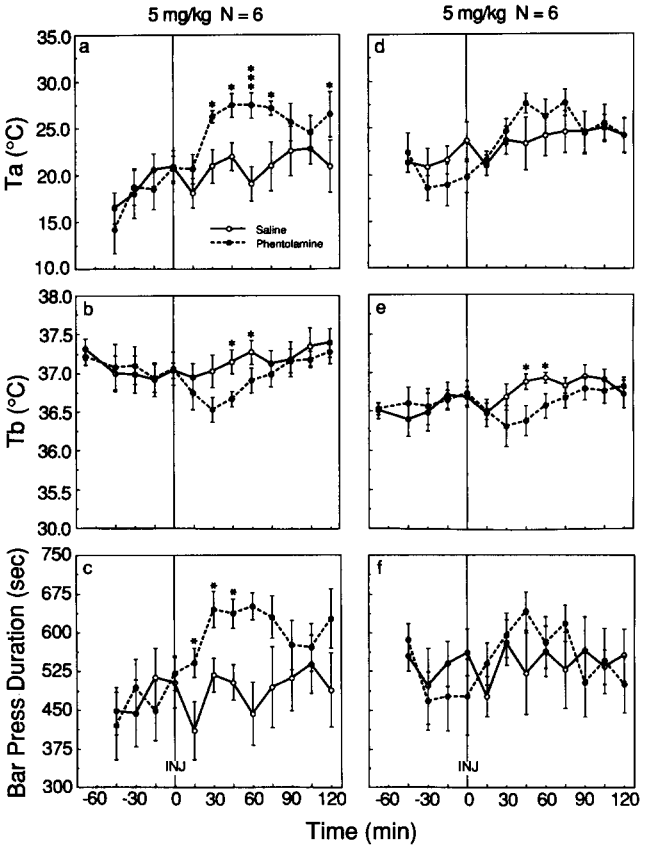

FIG. 2. Same as Fig. 1 after injection of PHEN (5 mg/kg).

were 0.5°C higher than controls' when rats were not given access to the bar in the heat (Ta 40°C), but this was not significant.

After PHEN (5 mg/kg) at the Tb peak, rats did not begin to hold the bar down longer to lower the Ta until 90 min postinjection. The Ta previously had risen to 32.7 °C, which occurred after Tb declined (Fig. 4 a–c). The drop in Tb that occurred between 30–45 min postinjection, 0.4°C, (Fig. 4b) was correlated with the Ta during the previous 15 min ($r = .96$; $p<0.005$). At the Tb trough, there were hardly any differences between drug and control groups with respect to any measure (Fig. 4c and d). There were no differences in Tb between rats with and without access to the bar.

DISCUSSION

To control for any sedative or excitatory effects of PHEN, the rats were run in two conditions. In the cold-escape, if they wanted to increase Ta, they had to barpress more for heat. In the heat-escape, if they wanted to increase Ta, they had to barpress less. In heat-escape their barpressing maintained the Ta at almost the same levels as did controls. After 10 mg/kg, Tb decreased about 0.6°C. This drop in Tb is most likely attributable to the 2°C drop in Ta that occurred in the first 15 min post-PHEN. A drop in Ta of 2°C, from 31° to below 29°C, may not seem important. However, we had earlier observed that post-PHEN (10 mg/kg) Tb did not fall at Ta 32°, but did at Ta 30°C (11,12). In the cold-escape situation, the rats did decrease their rate of barpressing in three of the four conditions for the first 15 min postinjection. After this, they worked for significantly higher Ta's than did controls. In other words, the decreases in Tb post-PHEN were eventually counteracted behaviorally.

The results in the first few minutes post-PHEN could be interpreted as a decrease in thermal set-point. The rats increased or decreased their response rate appropriately to lower Ta, and consequently their Tb fell. However, we believe the results are better explained by peripheral vasodilation after PHEN, an effect seen in rats (13), dogs (10), baboons (8) and humans (22). Peripheral vasodilation causes an increase in skin temperature. In fact, "a sensation of warmth with flushing of the skin" was the only effect reported by humans after intravenous injection of PHEN [5 mg; (9)]. Weiss and Laties (24) demonstrated that rats use operant thermoregulation to maintain a constant peripheral temperature. Furthermore, skin temperature is given 2–3 times the weight of hypothalamic temperature in determining operant response rate (6). Immediately post-PHEN, skin temperature increases at Ta 20–22°C [(13), Kent and Satinoff, unpublished observations]. Consequently, the sharp drop in Ta in the cold-escape after 10 mg/kg is most probably a response to a warm skin. The reduction in Ta allows enough heat to be lost for Tb to fall, and when this fall is sufficiently large, more than 0.5°C, the rats work harder than controls to warm themselves. In the heat-escape condition at Ta's near 30°C, skin temperature is already high, and PHEN does not increase it further (13). Consequently, Ta is not lowered and Tb does not fall.

These results agree with those of Schulze and colleagues,

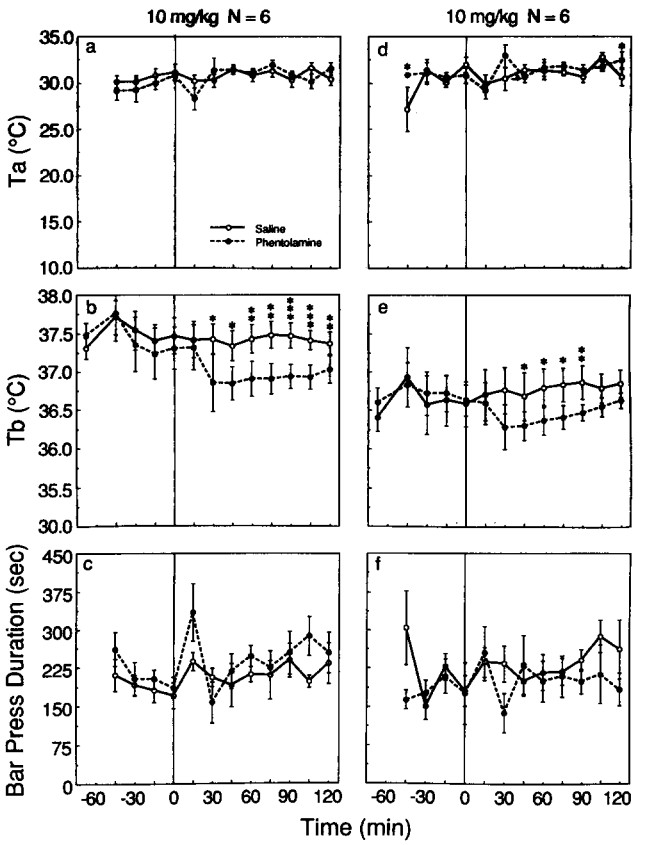

FIG. 3. Same as Fig. 1 in the heat-escape tests.

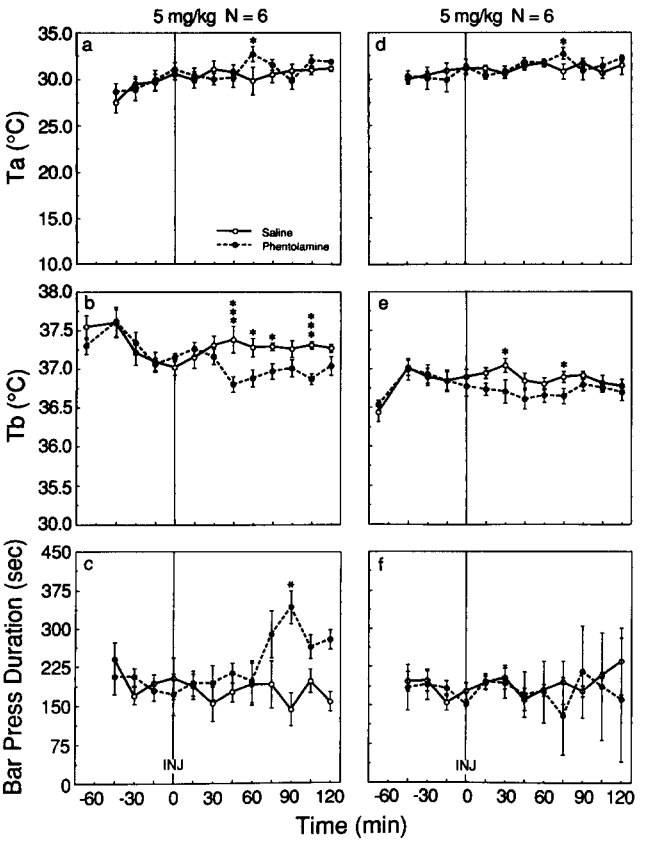

FIG. 4. Same as Fig. 1 after injection of PHEN (5 mg/kg).

who studied the thermoregulatory behavior of young and old rats (19) and rats with anterior hypothalamic lesions (20) after various doses of PHEN. They also found a dose- and Ta-dependent decrease in Tb and increase in Ta post-PHEN. But the problem still remains of whether the decrease in Tb was solely caused by increased heat loss or by a concomitant decrease in heat production, or by different mechanisms at different Ta's. If the latter, indicating integrated thermoregulatory responses, this would imply a transient decrease in thermal set-point. In Experiment 2 we measured these responses.

EXPERIMENT 2: HEAT LOSS AND HEAT PRODUCTION

This experiment sought to determine if the decrease in Tb after PHEN was caused by increased heat loss or decreased heat production or both, and whether the autonomic responses depended on the Ta.

METHOD

General Procedure

Tb, heat loss and heat production were measured in seven rats for at least 75 min prior to and 2 h after IP injections of PHEN HCl (10 mg/kg) in 1 ml isotonic saline or an equivalent volume of saline alone. Injections were administered after a stable baseline was obtained for all 3 measures. Six rats were injected once with PHEN and once with saline at Ta's of 2 and 20°C. Four of these were also injected at 30°C, but, because the Mini-Mitter stopped transmitting in the other two, another rat was tested at 30°C. All injections were separated by at least 2 days with at least 4 days between PHEN injections. All injections were made 3–9 h after lights-on.

Apparatus

The rats were placed in a small wire cage (26.5 × 11.5 × 11 cm) inside a gradient layer calorimeter (Model SEC-A-1201, Thermonetics Corporation, San Diego, CA), which provides a voltage output directly proportional to the rate of dry heat loss. The calorimeter was housed inside a temperature-controlled chamber. Water at the appropriate Ta (2, 20, or 30°C) was circulated through a jacket separating the inner and outer walls of the calorimeter to maintain a constant inside temperature of ±0.5°C. Air was circulated through the calorimeter at 4 l/min.

The air leaving the calorimeter was dried in columns of $CaSO_4$ desiccant and a small sample was shunted to an O_2 analyzer (Model S-3A, Applied Electrochemistry, Sunnyvale, CA) whose output was recorded by microcomputer. Calibration with a gas mixture of known composition was performed routinely. Flow rate was monitored with a mass flowmeter (Matheson Gas Products, East Rutherford, NJ) and corrected to STPD. Heat production was calculated from O_2 consumption assuming a caloric equivalent of 20 J of heat per 1.0 ml of O_2. The amount of heat extracted from the calorimeter by the flowing air was less than 5% of the heat dissipated by an average rat. The O_2 analyzer was calibrated at the beginning and end of each test. Any drift from baseline was assumed to be linear and an incremental correction was applied from the first min of recording

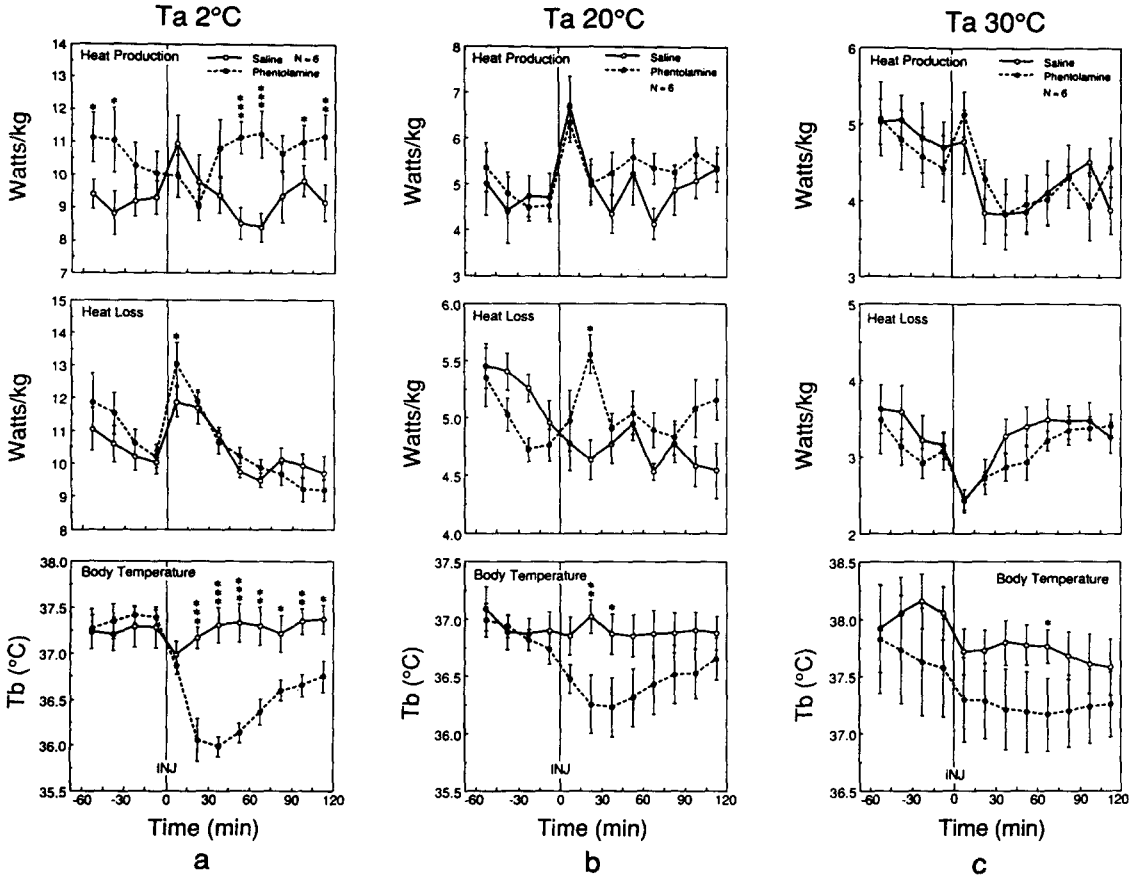

FIG. 5. Fifteen-min averages of heat production, heat loss, and Tb for 60 min pre- and 120 min postinjection of saline and PHEN (10 mg/kg IP) at Ta (a) 2°C, N=6 (b) 20°C, N=6 (c) 30°C, N=5. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

until the last. In addition, a correction was applied to the heat loss values for the first 15 min after opening the calorimeter because of the difference in Ta between the room and calorimeter. The amount of the correction was determined for each Ta by mimicking the injection procedure. At all Ta's, the correction had an exponential function with the first 5 min accounting for at least 67% of the displacement.

Data Collection and Analysis

Tb, heat loss, and O_2 consumption values were recorded and displayed by a microcomputer at 1 min intervals and stored on disk. Data were analyzed in 15 min blocks using a within-subjects 3-way ANOVA. A 2 (treatments: saline and PHEN) × 3 (Ta's: 2, 20, and 30°C) design was used with repeated measures on the 4 pre- and 8 postinjection 15 min blocks. Differences between the three Ta's were determined by the Tukey test. Planned comparisons were conducted at each Ta and each block to determine significant differences between saline and PHEN.

RESULTS

Overall Summary

Preinjection levels of heat production ($p<0.001$), heat loss ($p<0.001$), and Tb ($p<0.025$) were all Ta dependent. Heat production was highest at 2°C and similar at 20 and 30°C. Heat loss was also highest at 2°C and lowest at 30°C. Tb was higher at 30° than at 20°C. Rats injected with saline increased heat production for the first 15 min at both 2° and 20°C; heat loss was only increased at 2°C. Tb did not change at any Ta.

The effect of PHEN on heat production and heat loss were also Ta dependent. At Ta 2°C, Tb was decreased primarily by a large increase in heat loss without a change in heat production. The increase in heat loss at Ta 20°C was not as large, but heat production was increased. Consequently, Tb dropped very little. At Ta 30°C, neither PHEN nor saline had an effect on any measure.

Ta 2°C

Heat production was similar for both groups of rats during the first 45 min postinjection. In the first 15 min after PHEN heat loss increased above control levels ($p<0.02$). After this there were no differences between groups. When Tb had dropped almost 1°C, heat production increased above control levels for the next 75 min (Fig. 5a). Heat loss gradually decreased for the rest of the recording period.

By 30–45 min after PHEN, Tb dropped 1.4±0.1°C from preinjection levels. Then it slowly increased, and by the end of the 2 h recording period it was 0.5±0.1°C below control levels. Except for the first 15 min, Tb was significantly decreased compared to controls for the entire 2 h session ($p<0.02$ to 0.001). Tb was not altered postsaline.

Ta 20°C

Heat production was not significantly different in the two groups of rats. After PHEN, heat loss increased from 4.77 ± 0.14 to 5.56 ± 0.17 W/kg within 15–30 min ($p<0.05$; Fig. 5b). Mean Tb was 0.7–0.6°C below controls 15–45 min post-PHEN ($p<0.01$ and 0.05). However, only 3/6 rats decreased Tb more than 0.3°C. There appeared to be 2 distributions of rats at this Ta: those that increased heat production in response to the increased heat loss, and whose Tb did not change, and those that did not and whose Tb fell.

Ta 30°C

Heat production and heat loss did not differ between controls and rats injected with PHEN (Fig. 5c). Tb's differed by 0.5°C for most of the pre- and postinjection period and only at one point, 60 min postinjection, was this significant.

DISCUSSION

These results demonstrate that falls in Tb after PHEN were due to an increase in heat loss with no concomitant decrease in heat production. Indeed, at 2°C, heat production increased significantly, and the time course of the rise implies that heat production was compensating for increased heat loss in an attempt to maintain Tb. This argues that PHEN is not lowering thermal setpoint.

To our knowledge there have been only two other studies that measured reflexive thermoregulatory responses after PHEN. Rothwell et al. (17) found no change in O_2 consumption after 5 mg/kg at Ta 29°C. Lin et al. (13) using restrained rats and lower doses, found a dose-dependent fall in Tb at Ta's of 22 and 8°C. At 8°C, hypothermia was produced solely by a decrease in metabolic rate. At 22°C, the hypothermia was caused by increased cutaneous vasodilation and decreased metabolic rate. At 30°C, there were no changes in any measure. Because different effectors were used at different Ta's to produce the drop in Tb they concluded that the lowered Tb was produced by "a specific mode of action," which implies an integrated and coordinated response of the thermoregulatory system and a central site of action. However, it could well be that the restraint the rats were under caused them to maintain vasoconstriction, even in the face of noradrenergic blockade, through some other chemical pathway.

EXPERIMENT 3: CHANGES IN TB AFTER ICV INJECTIONS OF PHENTOLAMINE

This experiment sought to determine if the effects of peripherally administered PHEN on Tb were due to a central site of action. Cantor and Satinoff (3) had reported that ICV injections of PHEN (2 μg) had no effect on brain temperature in rats. In this experiment we used doses comparable to those of Lin et al. (13) to see if they would cause changes in Tb.

METHOD

General Procedure

Six rats were housed individually in Plexiglas cages (24.5 × 22 × 21 cm) in a room maintained at 24 ± 1°C. Tb was recorded every 10 min for 30 min before and 180 min after ICV injections of PHEN or saline at Ta 24 and 0°C. All injections were made 2–4 h after lights-on. Each rat was injected once with saline and once with each dose of PHEN. At least 2 days separated saline and PHEN injections and at least 4 days separated PHEN injections. The rats were handled frequently for at least 2 weeks prior to the injections to accustom them to the procedure.

Surgery

Rats were anesthetized and implanted stereotaxically with a guide cannula made from 21-gauge stainless steel (ss) tubing, and placed 0.5 mm above the right or left lateral ventricle. Solid 28-gauge ss wire cut flush with the tip of the guide cannula rested in the guide between injections. Three ss jeweler's screws were threaded through holes drilled in the skull and anchored to the skull with dental acrylic. Coordinates for cannula placement were 1.5 mm lateral and 0.5 mm posterior to bregma, and 2.5 mm ventral to the skull surface according to the atlas of Paxinos and Watson (16). At this time, a temperature telemetry device was also implanted IP. At the end of the procedure, all rats were injected intramuscularly with 30,000 U of penicillin.

Drug Injections

A rat was taken out of its home cage and the stylet was removed from the guide cannula and replaced with an injection cannula whose tip protruded 1 mm below the tip of the guide cannula. The injection cannula was attached to a Hamilton 25 microliter syringe through polyethylene tubing. Both the tubing and the injection cannula were flushed with 100% ethanol and sterile saline before each injection. Injections were delivered slowly over a 60 s period, and the injection cannula was left in the guide for an additional 30 s after the injection was complete. Drugs used were PHEN HCl (10 and 20 μg in 4 μl or 50 μg in 8 μl isotonic saline), PHEN mesylate (100 μg in 8 μl), or saline (4 μl). In addition, each rat was injected with PHEN HCl (50 μg in 4 μl) at Ta 0°C. At the end of the experiments, the rats were given an overdose of Ketaset and perfused through the heart with 0.9% saline and 10% formalin solution. Cannula placement was verified by injecting a solution of India ink into the injection cannula and then slicing the brain after removal from the skull.

Data Collection and Analysis

Tb data were collected and stored every 10 min. Data were analyzed in 30 min blocks using a 2-way ANOVA with repeated measures on the 2 pre- and 6 postinjection blocks. Differences between each of the five treatments and saline were determined by the Dunnett test.

RESULTS

Tb increased after all injections, and there were no significant differences between saline or any dose of PHEN at 24°C (Fig. 6). Furthermore, there was no dose-response relationship observed. There were no significant effects seen between saline and PHEN (50 μg) at Ta 0°C.

DISCUSSION

The results of this experiment argue against a central site of action for the decreased Tb seen after peripheral administration of PHEN. Tb was not lowered at any dose or Ta, and in fact, Tb increased slightly more than it did in controls. Previous work concerning the effects on Tb of ICV PHEN has produced varied results. PHEN (20–50 μg) has been reported to lower Tb at a Ta of 22°C (13). At a dose sufficient to block the hypothermic effects of 2 μg NE, ICV PHEN (2 μg) did not alter Tb (3). A

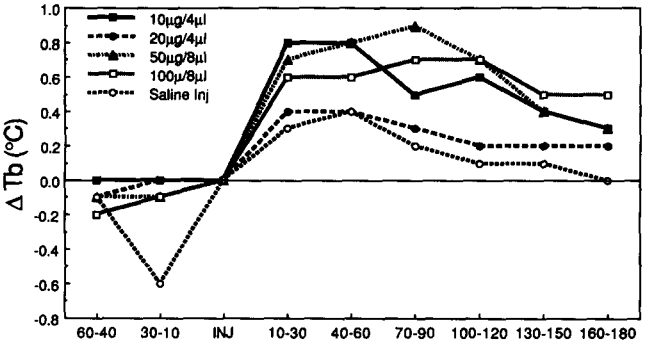

FIG. 6. 10 min averages of the change in Tb for 120 min postinjection of (a) saline and (b) PHEN (10 and 20 µg ICV).

recent bibliography on the effects of noradrenergic agents on Tb contained 6 references for ICV PHEN (5–40 µg; Ta 19–26°C) in rats: 3 reported no change in Tb and 3 reported decreases of 0.6–0.7°C (4). Even within the same laboratory, at 22°C, Tb decreased 0.6°C after ICV injection of 5 µg PHEN (15) yet there was no change in Tb after 10 µg (14). Results from microinjections of PHEN into the preoptic area of rats are not any clearer. PHEN (10 µg) elevated Tb by 1°C for at least 1 h during lights-out (7). A larger dose (40 µg) administered during lights-on did not change Tb (23).

It may be that PHEN cannot even cross the blood-brain barrier. Only indirect evidence exists on this point, but it suggests that PHEN penetrates the brain poorly, if at all. PHEN (10 and 5 mg/kg IP) did not alter turnover of norepinephrine in the brain or spinal cord of rats (1). Baraban and Aghajanian (2) examined the suppression of firing activity of serotonin neurons by α-adrenoceptor antagonists in rats. They found that PHEN produced a large suppression when applied iontophoretically; no effect was seen after intravenous doses of up to 10 mg/kg.

GENERAL DISCUSSION

The results of the three sets of experiments demonstrate that decreased Tb after IP injection of PHEN is due to one main action of the drug; increased heat loss caused by peripheral vasodilation. When rats were allowed to work to regulate the Ta, they raised Ta soon after Tb fell, and Tb had returned or was getting closer to baseline levels by 2 h postinjection. When rats were not allowed to control Ta, Tb dropped precipitously in the cold and increased more than controls' Tb in the heat. If the PHEN-induced fall in Tb had been caused by integrated thermoregulatory responses, then warmer Ta's should have been more stressful and the rats should have worked to lower the Ta. This is not what we found. If PHEN lowers Tb by altering a specific thermoregulatory effector, then the zone of thermal comfort should be raised and rats should work to raise the Ta. This is exactly what we found.

Furthermore, we found that the major effect of PHEN was to increase heat loss. Heat production was actually elevated in the cold after Tb had fallen. This is the opposite of integrated thermoregulatory responses. Finally, there was no change in Tb after central injections of a wide dose range of PHEN.

In summary, these results demonstrate that peripheral administration of PHEN lowers Tb by increasing heat loss without affecting heat production. In the initial 15–30 min postinjection, in the cold the rats did not work as hard to keep the Ta up and in the heat they worked harder to lower Ta. We favor the hypothesis that this is caused by high skin temperature. When core temperature had fallen about 0.5°C the rats worked to offset the fall. In addition, in the cold, heat production increased while Tb was lower than normal. These unintegrated responses seem to be mediated peripherally as central injections of PHEN had no effect on Tb.

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