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Effect of Ambient Temperature on the Paradoxical Metabolic Responses to Norepinephrine

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ZYLAN, K. D. AND H. J. CARLISLE. *Effect of ambient temperature on the paradoxical metabolic responses to norepinephrine.* PHARMACOL BIOCHEM BEHAV 43(2) 577–582, 1992.—Four experiments were conducted to examine the effect of ambient temperature (T_a) on norepinephrine (NE)-induced metabolism. NE increased oxygen consumption at ambient temperatures above and at acclimation temperature and decreased oxygen consumption at ambient temperatures below acclimation temperature in both nonacclimated (25°C) and cold-acclimated (5°C) rats. Varying the T_a between −5° and 25°C at a fixed dose of NE (250 μg/kg, IP) resulted in a temperature-dependent decrease in metabolism in nonacclimated rats as a function of T_a. A similar effect was demonstrated in cold-acclimated rats tested at −15, 5, and 25°C. Varying the dose of NE between 100 and 1,000 μg/kg at a T_a of 25°C resulted in a maximal thermogenic response at a dose of 250 μg/kg with diminished responsiveness at higher and lower doses. At 5°C, NE inhibited metabolism maximally at a dose of 250 μg/kg. Propranolol, a nonspecific β-antagonist, attenuated the hypometabolic effect of NE in the cold, while the α_2-antagonist yohimbine completely blocked this effect. These results suggest that the metabolic suppressive effect of NE may be mediated by the presynaptic α_2-receptor and that β-adrenoceptors may also contribute to this effect.

Norepinephrine Nonshivering thermogenesis Oxygen consumption Brown adipose tissue
Yohimbine Propranolol Rat

NONSHIVERING thermogenesis, a primary autonomic means of temperature regulation in the rat, is mediated by the release of norepinephrine (NE) from the sympathetic nervous system (15–18). Brown adipose tissue (BAT) is richly innervated by this system and is the primary site for NE-induced nonshivering thermogenesis (8,10). NE stimulates BAT metabolism by facilitating lipolysis, which yields the fatty acids necessary for uncoupled respiration in the adipocyte mitochondria (3). The role of NE in the stimulation and maintenance of BAT thermogenesis has been well established [see (16,19,29) for reviews], and peripheral injections of NE are often used to assess BAT functioning (6,10,14,22–24,27,28). We recently found, however, that NE produces paradoxical effects when animals are tested in a cold environment (36). Rats increased the amount of heat obtained in a behavioral test at −8°C, while oxygen consumption was suppressed by NE at 5°C. These results are difficult to reconcile with the established thermogenic capacity of NE. If NE is the mediator of cold-induced nonshivering thermogenesis, why then should exogenous NE antagonize metabolic responsiveness in the cold? One possibility is that peripheral adrenoceptors are differentially activated by the combination of cold and exogenous NE. The paradoxical effects of NE have also been observed for the mixed β_1/β_2-adrenoceptor agonist isoproterenol (4). Isoproterenol, like NE, is a potent thermogenic agent, yet it produces profound hypothermia despite increased behavioral responding for external heat in cold-exposed rats. These particular results suggest the paradoxical effects of thermogenic agonists may be mediated by β-receptors. However, the participation of the presynaptic α_1-receptor, which regulates NE production and release (21,32), must also be considered. Because cold exposure stimulates the endogenous release of NE, it is possible that further injection of NE may stimulate this negative feedback mechanism, inhibiting BAT thermogenesis.

The present study was designed to examine the conditions and parameters necessary for the paradoxical metabolic effects of NE in the cold and further to assess the roles of the adrenoceptor subtypes in mediating these effects.

METHOD

Animals

Male Sprague-Dawley rats (N = 96) were obtained from Bantin-Kingman (Fremont, CA). They were housed individu-

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ally in wire-mesh cages in a colony room maintained at 23°C with a relative humidity of 50% and a 12 L:12 D cycle (lights on at 0700 h). All tests were conducted during the light phase of the cycle. Animals were given free access to Purina Rat Chow (5001) and water. Cold-acclimated rats were maintained in the same wire-mesh cages in a room maintained at 5°C with free access to chow and water for a period of at least 2 weeks prior to testing and for the duration of the experiment.

Metabolic Measurements

Oxygen consumption was measured by the open-circuit method. The experimental chamber was a 4-l spherical plastic container through which air was drawn at a flow rate of 3–4 l/min. A sample of this air was dried and passed to a Beckman Oxygen Analyzer (Model OM-11, Beckman Instruments, Fullerton, CA) before recombining with the total airflow. The air was then dried again and passed through a dry gas meter (American Singer, New York, NY) for the measurement of airflow. Measurements were collected on a strip-chart recorder (Microscribe 4500, Houston Instruments, Houston, TX), analyzed for 5-min intervals, and corrected to standard temperature and pressure (0°C, 760 mm Hg, dry). Oxygen consumption data (ml O_2/min) were converted to watts using 1 ml O_2/min = 0.337 W [where 0.337 is the product of the respiratory equivalent of 4.83 cal/ml O_2 for a mixed diet (2) and the conversion factor 1 W = 0.069733 cal/min]. Data are expressed as W/kg to correct for differences in body mass. The experimental chamber was housed in a thermostatically controlled room for the 5, 15, and 25°C conditions and in a Kelvinator (Manitowoe, WI) freezer for the −5 and −15°C conditions. Ambient temperature (T_a) was maintained with an accuracy of ±2°C. Colonic temperature was measured prior to and at the end of a session with a Sensortek (Clifton, NJ) BAT-12 meter and thermocouple probe inserted 6–7 cm.

Drugs

(-)-Norepinephrine bitartrate (Levophed, Winthrop-Breon, New York, NY), (±)-propranolol HCl (Sigma Chemical Co., St. Louis, MO), and yohimbine HCl (Sigma), mixed with a saline vehicle, were administered IP. All doses were calculated as the base. Control animals were injected IP with the vehicle in an equivalent volume (1 ml/kg). When two drugs were administered together, the antagonist preceded the agonist by several minutes.

Protocol

Four experiments utilized the same general protocol. Rats were given one 60-min adaptation session at their acclimation temperature to familiarize them with the test apparatus. Test sessions consisted of 30 min of baseline testing followed by injection of the appropriate drug and an additional 60-min test period. Number of test sessions varied with each experiment. All test sessions were conducted during the light phase of the cycle and were separated by at least 1 week.

Experiment 1 examined the effect of a standard dose of NE (250 μg/kg) on oxygen consumption at four ambient temperatures: −5, 5, 15, 25°C. Twenty-four rats were randomly assigned to one of the four test temperatures and received one 90-min test session at this T_a. In Experiment 2, animals (n = 12) acclimated to 5°C were injected with NE or saline, depending upon group assignment, and tested at temperatures below (−15°C), at (5°C), and above (25°C) the acclimation temperature in a counterbalanced order. Experiment 3 examined the effect of varying the dose of NE (0, 100, 250, 500, and 1,000 μg/kg) at a neutral (25°C) and cold (5°C) ambient temperature. Rats (n = 50) were assigned to one of five groups corresponding to the five doses of NE and were given one test session at each T_a in a counterbalanced order. Experiment 4 examined the roles of the adrenoceptor subtypes in the mediation of the paradoxical response to NE. Fifty rats were randomly assigned to the following drug conditions: saline, NE (mixed α/β-agonist), propranolol (β-antagonist), NE + propranolol, or NE + yohimbine (α_2-antagonist). Each rat received two test sessions, one at 25° and one at 5°C. All drugs were administered in equimolar concentrations corresponding to the concentration of NE at the 250-μg/kg dose (1.4 μM/kg). These doses were thus 363 μg/kg for propranolol and 496 μg/kg for yohimbine. Some of the experiments above contain duplicate conditions (i.e., same drug, dose, and T_a); these duplicate conditions were not repeated for each experiment. Thus, data from a single group of nonacclimated animals injected with 250 μg/kg NE and tested at 25° and 5°C and a single group of saline controls tested at 25° and 5°C were used in the analyses in Experiments 3 and 4.

Data Analysis

Standard test duration of 90 min consisted of a 30-min adaptation baseline followed by injection and an additional 60-min test. Oxygen consumption data were analyzed as difference scores (test minus the last 15 min of baseline). The first 15 min of baseline were not used to avoid inclusion of data that contained high activity levels associated with exploratory behavior. Analyses of variance (ANOVAs) were conducted on metabolic mean difference scores (test minus baseline) over the 60-min test. When warranted, posthoc tests were conducted using Fisher's least significant differences (LSD) test (20). Similar analyses were used for data derived from core temperature measurements.

RESULTS

Experiment 1: Ambient Temperature

During baseline testing, oxygen consumption increased as T_a decreased, as shown in Table 1, indicating that 30 min of cold exposure was sufficient to induce a significant thermogenic response, $F(3, 20) = 40.88$, $p < 0.05$. Figure 1 shows the overall effect of NE on metabolic rate at each T_a. Oxygen consumption increased at 25°C, but decreased at lower temperatures. The lower the T_a, the greater the decrease in oxygen consumed, $F(3, 20) = 15.33$, $p < 0.001$. Core temperature (T_c) fell significantly at temperatures below acclimation (15, 5, −5°C), $F(3, 20) = 3.14$, $p < 0.05$. However, the fall in T_c was no greater at −5 (−2.13°C) and 5°C (−2.17°C) than at 15°C (−2.35°C).

TABLE 1

MEAN (±SEM) BASELINE METABOLIC RATE AS A FUNCTION OF AMBIENT TEMPERATURE (T_a)

T_a (°C)	n	Metabolic Rate (W/kg)
− 5	6	17.16 (±0.79)
5	6	15.14 (±1.05)
15	6	10.89 (±0.68)
25	6	5.80 (±0.55)

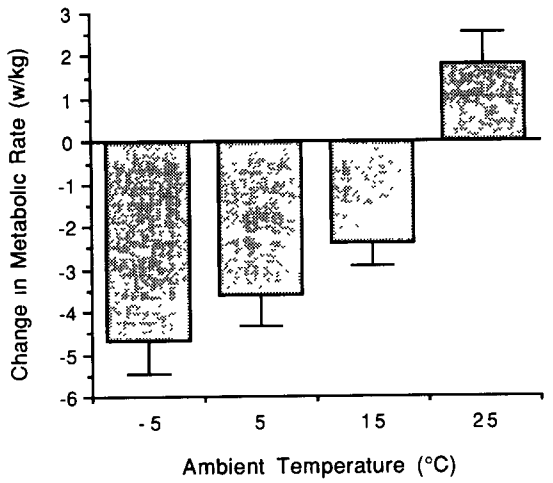

FIG. 1. Change in metabolic rate following a dose of NE of 250 μg/kg as a function of ambient temperature (n = 6).

Experiment 2: Cold Acclimation

As in Experiment 1, baseline metabolic rate varied significantly with T_a, $F(2, 20) = 129.50$, $p < 0.001$. The mean values for baseline metabolic rate at −15, 5, and 25°C were 20.73, 9.73, and 7.12 W/kg, respectively. As shown in Fig. 2, ambient temperature significantly affected the metabolic response to NE such that oxygen consumption increased when animals were tested at or above acclimation temperature but decreased when tested below acclimation temperature. There was a significant main effect for temperature, $F(2, 20) = 13.24$, $p < 0.001$, as well as a significant effect of temperature on NE-treated animals, $F(2, 20) = 10.91$, $p < 0.001$, but not on saline controls. Similarly, NE increased body temperature by 1.42°C at 25°C and decreased body temperature by 1.33°C at −15°C ($p < 0.05$). A slight (−0.7°C) decrease in T_c was noted at 5°C despite the increased metabolic rate.

Experiment 3: Dose-Response

One half the animals injected with the highest dose (1,000 μg/kg) of NE died during the tests. Three died during the 25°C test and two during the 5°C test. Death occurred rapidly, usually within 5 min following injection. It is likely that death resulted from the cardiovascular effects of the drug.

All groups irrespective of drug treatment showed a significantly higher preinjection baseline metabolic rate in the cold ($p < 0.01$). Ambient temperature significantly altered the metabolic response to NE, $F(1, 40) = 114.02$, $p < 0.001$, as shown in Fig. 3. All doses increased oxygen consumption at 25°C, while decreasing oxygen consumption at 5°C. At 25°C, only a dose of 250 μg/kg significantly increased metabolic rate above control levels ($p < 0.05$). Nevertheless, the dose-response curve at 25°C clearly shows a trend toward an inverted U-shaped function. In contrast, all doses of NE produced a significant decrease in oxygen consumption when animals were tested at 5°C ($p < 0.05$ or less). Although a dose of 100 μg/kg was sufficient to markedly decrease metabolism, higher doses produced significantly greater decreases ($p < 0.05$). Figure 4 shows that T_c fell significantly as a function of the NE dose at 5°C, whereas there was a slight hypothermic effect at 25°C that was maximal for the 500-μg/kg dose.

Experiment 4: Adrenoceptor Agonists/Antagonists

As in all of the previous experiments, baseline oxygen consumption varied significantly as a function of T_a, $F(1, 45) = 153.36$, $p < 0.001$. Baseline metabolic rate averaged 8.1 W/kg at 25°C and 12.77 W/kg at 5°C with no differences between groups as a function of drug assignment.

ANOVA of the mean change in oxygen consumption over the 60-min session revealed significant main effects for drug group, $F(4, 45) = 7.11$, $p < 0.001$, and T_a, $F(1, 45) = 34.91$, $p < 0.001$, as well as a significant interaction, $F(4, 45) = 7.34$, $p < 0.001$. Figure 5 illustrates the effects of the adrenergic agonists and antagonists on metabolic rate at 25 and 5°C. NE alone and NE coadministered with yohimbine showed paradoxical metabolic effects that were dependent

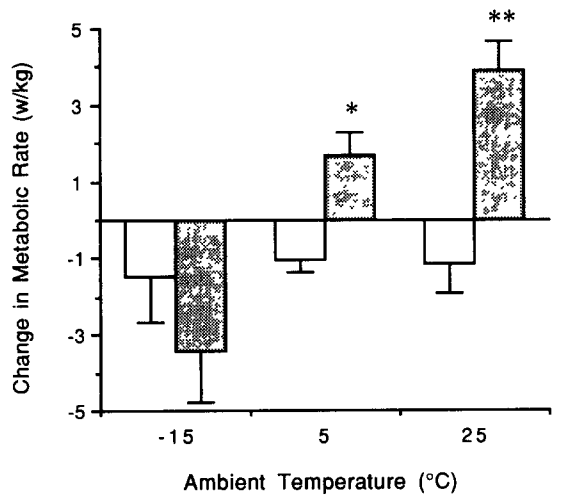

FIG. 2. Change in metabolic rate following saline (open) or 250 μg/kg NE (shaded) in acclimated rats tested at temperatures below, at, and above acclimation temperature. *$p < 0.05$, **$p < 0.01$ compared to saline (n = 6).

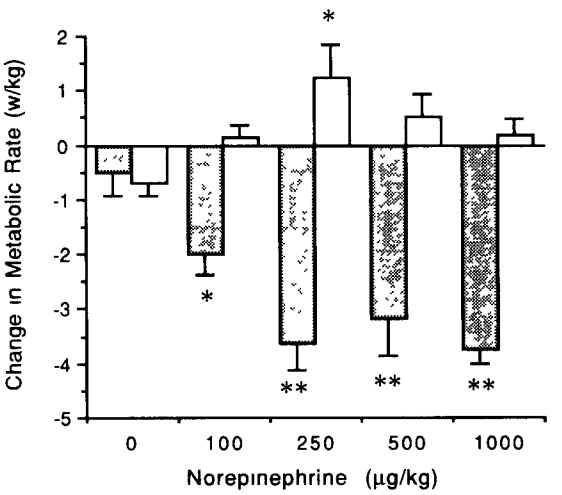

FIG. 3. Change in metabolic rate following different doses of NE tested at either 5°C (shaded) or 25°C (open). *$p < 0.05$, **$p < 0.01$ compared to saline (n = 10 in all groups except 1,000 μg/kg, where n = 5).

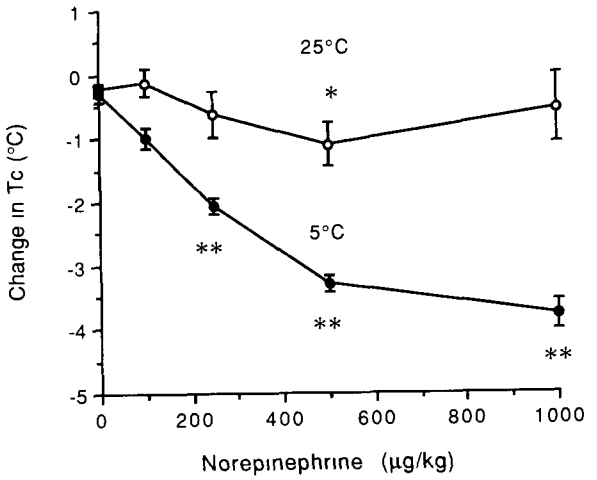

FIG. 4. Change in posttest colonic temperature (T_c) following different doses of NE at two ambient temperatures. *$p < 0.05$, **$p < 0.01$ compared to saline ($n = 10$ in all groups except 1,000 µg/kg, where $n = 5$).

upon T_a. For both drug conditions, oxygen consumption increased at 25° and decreased at 5°C, although the decrease resulting from NE plus yohimbine was significantly less (−0.70 W/kg) than that from NE alone (−3.61 W/kg) ($p < 0.001$). Despite the ability of yohimbine to block the hypometabolic effect of NE at 5°C, T_c fell significantly as shown in Table 2.

Propranolol alone had little effect on metabolic rate. However, coadministration with NE attenuated the usual hypometabolic effect of NE at 5°C, although the decrease in T_c was similar to that seen when NE was administered alone. Propranolol also reversed the hypermetabolic effect of NE at 25°C and significantly decreased T_c.

DISCUSSION

The results of this study clearly demonstrate the paradoxical nature of the metabolic effect of NE. NE stimulates metabolic heat production when animals are tested at ambient temperatures at or above their acclimation temperature but inhibits metabolism below acclimation temperature. This inhibitory effect is both dose and temperature dependent.

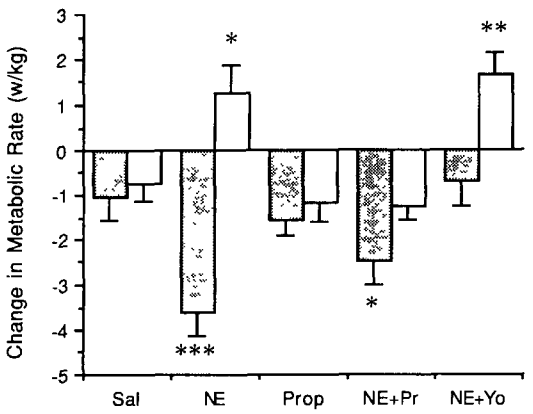

FIG. 5. Change in metabolic rate following administration of saline (sal), norepinephrine (NE), propranolol (Prop & Pr), and yohimbine (Yo) at 5°C (shaded) or 25°C (open). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to saline ($n = 10$).

TABLE 2

MEAN (±SEM) CHANGE IN COLONIC TEMPERATURE (T_c) FOLLOWING VARIOUS DRUG TREATMENTS AT 5°C AND 25°C

	n	T_c @ 5°C	T_c @ 25°C
Saline	10	−0.25 (±0.13)	−0.21 (±0.10)
NE	10	−2.06 (±0.15)*	−0.62 (±0.36)
Propranolol	10	−0.04 (±0.15)	−0.17 (±0.08)
NE + Propranolol	10	−1.98 (±0.51)*	−1.10 (±0.22)*
NE + Yohimbine	10	−1.60 (±0.31)*	0.05 (±0.29)*

*$p < 0.05$ compared to saline.

Changes in environmental temperature have been shown to alter the toxicity, magnitude, and direction of effect in many drugs (12). Amphetamine, for example, shows a similar temperature-dependent paradoxical thermogenic effect as NE. Amphetamine increases body temperature in a warm environment and decreases body temperature in a cold environment (34). Other drugs that exhibit this pattern include: lysergic acid diethylamide-25, reserpine, 5-hydroxytryptamine, chlorpromazine, fenfluramine, and isoproterenol (1,4,35). Isoproterenol produces paradoxical effects in both behavioral and physiological thermoregulation (4). These paradoxical effects have been attributed to the β_2-receptor because they are blocked by β_2-antagonists and exacerbated by β_1-antagonists (5). While β_2 involvement in the present study may be part of the paradoxical effects of NE, it does not appear that this receptor is solely responsible for these effects for several reasons. First, the paradoxical effects of isoproterenol can be completely blocked by a dose of propranolol of 100 µg/kg (5). However, in the present study (Experiment 4) a dose of propranolol of 363 µg/kg attenuated but did not reverse the inhibitory effect of NE, suggesting that β-receptors may participate in this inhibition but are not responsible for the entire effect. Moreover, the strong effects of yohimbine in reversing the hypometabolic effect of NE suggests that the α_2-subtype, perhaps a presynaptic autoreceptor, may mediate this effect. This would seem likely because yohimbine preferentially blocks presynaptic α_2-receptors (9) and stimulation of these adrenoceptors is known to inhibit the release of NE (21), which would impair BAT thermogenesis. Although a presynaptic α_2-adrenoceptor has not been identified in BAT, clonidine (an α_2-agonist) has been shown to inhibit lipolysis and respiration in brown adipocytes (33).

Because endogenous levels of NE are inversely proportional to ambient temperature (31), if the hypothesis of a presynaptic autoreceptor were correct it would be expected that the inhibitory action of NE would likewise be inversely proportional to ambient temperature. This expectation was supported by the finding that NE inhibited metabolism at all temperatures below room temperature and did so in a graded fashion (Experiment 1). Consistent with this finding, the results of Experiment 2 showed that cold-induced thermogenesis interfered with the metabolic effect of exogenous NE in cold-acclimated rats, which typically show a large increase in metabolism when injected with NE (6,7,17). This finding concurs with an earlier report in which cold-acclimated animals demonstrated an attenuated increase in metabolism in response

to NE when tested at an ambient temperature below room temperature but above acclimation temperature (26). Furthermore, the results of Experiment 3 showed that high doses of NE are less effective in stimulating metabolism when animals are tested at 25°C, a temperature at which endogenous release is minimal. This finding suggests that high levels of NE may, in fact, induce an inhibitory mechanism.

Experiment 4 provides some evidence that this inhibitory mechanism may well be the presynaptic α_2-adrenoceptor because yohimbine completely blocked the inhibitory action of NE in the cold. It should be noted, however, that yohimbine readily penetrates the CNS (13). Therefore, it is possible that yohimbine exerts its protective action centrally and not specifically at a peripheral presynaptic autoreceptor.

Although it seems likely that the presynaptic autoreceptor mediates the inhibitory effect of exogenous NE in the cold, the nonthermogenic effects of NE must also be considered. Specifically, NE exerts considerable cardiovascular effects (13). Some mortality associated with high doses of NE assumed to be due to cardiovascular effects were noted in the present study. MacDonald and Siyamak reported a similar mortality rate (60%) in rats infused with NE at a rate of 4 and 8 μg/kg/min for 20 min each (25). This mortality was most likely associated with dose and not T_a because these experiments were conducted at 29°C. However, the cardiovascular effects of NE may be sensitive to ambient temperature as well. Hirata and Nagasaka reported a decrease in oxygen consumption in nonacclimated rats following NE infusion at 17°C with concomitant decreases in heart rate, cardiac output, and blood flow to BAT (15). In cold-acclimated rats, however, NE increased cardiac output and blood flow, particularly to BAT. These authors suggested that the changes in cardiovascular effects of NE infusion were directly related to the thermogenic action of the drug, that is, in nonacclimated rats the decreased blood flow diminished the effectiveness of NE-induced thermogenesis, while the increased blood flow enhanced the thermogenic effect of NE in cold-acclimated animals. The effects found in nonacclimated rats are not in agreement with previous research, which has found increases in cardiac output and blood flow to BAT in both cold- and nonacclimated rats (11). Because both studies utilized the same methods with the exception of ambient temperature, it is possible that this difference alone was responsible for the discrepancy in results. Thus, the cardiovascular effects, as well as the thermogenic effects, of NE may be significantly influenced by environmental temperature. It is not clear which of these effects participate in the metabolic inhibition seen in the cold; however, the results of a preliminary study (Zylan and Carlisle, unpublished results) indicate that the vasomotor effects of NE play a relatively small role because NE does not alter blood flow in the tail at 5°C.

In addition to its cardiovascular effects, NE also impairs shivering thermogenesis (30). Any or all of these effects may contribute to the paradoxical metabolic effect of NE. The results of the present study, however, indicate that the inhibitory effect of exogenous NE in the cold is mediated by the α_2-adrenoceptor. Whether or not this is a direct effect on BAT remains to be determined.

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