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BRIEF COMMUNICATION

The Influence of Hypothalamic Temperature on some Thermoregulatory Effects of Hypothalamic Injections of Norepinephrine[1]

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LAUDENSLAGER, M. L. *The influence of hypothalamic temperature on some thermoregulatory effects of hypothalamic injections of norepinephrine.* PHARMAC. BIOCHEM. BEHAV. 5(6) 713–716, 1976. – Bilateral injections of norepinephrine bitartrate (5.0–20.0 μg) into the preoptic region and anterior hypothalamus were always followed by a reduction in core temperature and rate of behaviorally obtaining radiant heat in cold-exposed (5°C) squirrel monkeys regardless of whether the temperature of this region was experimentally raised (40–42°C) or lowered (32–34°C). Decreases in tail temperature following injections of norepinephrine indicated that vasoconstriction was also associated with the reduction in body temperature and behavioral responses. Since conflicting behavioral and autonomic responses are observed following injections of norepinephrine, it is suggested that norepinephrine may be affecting thermoregulatory effector pathways nonspecifically rather than altering the set point about which body temperature is regulated.

Behavioral thermoregulation Hypothalamic temperature Hypothalamus Norepinephrine
Peripheral vasomotor tone Set point Squirrel monkey

THE significance of the preoptic region and anterior hypothalamus (PO/AH) in the control of thermal balance has been demonstrated both by local thermal stimulation [3,4] and by direct microinjections of putative neurotransmitters [2, 6, 8]. It has been suggested [2] that the regulation of body temperature might be dependent on a balance in the release of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) within the PO/AH, whereby 5-HT activates heat-production responses and NE either inhibits heat-production or activates a separate heat-loss pathway. Both ambient temperature (T_A) and PO/AH temperature ($T_{PO/AH}$) may influence the nature of the thermoregulatory responses which follow ventricular injections of NE in sheep [1,7]. At a warm T_A or during experimental elevation of $T_{PO/AH}$, NE inhibits panting, whereas at a cold T_A or during PO/AH cooling, injections of NE inhibit shivering. Thus, NE may inhibit both autonomic heat-production and heat-loss pathways. The present study briefly describes the lack of influence of $T_{PO/AH}$ on the behavioral thermoregulatory effects of PO/AH injections of NE in the squirrel monkey.

METHOD

Animals

Adult male squirrel monkeys, which had served as subjects in a previous study [4], were used. Each animal was implanted within the PO/AH with a bilateral thermode/cannula assembly that allowed for experimental displacement of $T_{PO/AH}$, PO/AH microinjections, or both concurrently.

Apparatus

Temperature measurement. Temperatures were measured with thermistors, which served as one arm of a Wheatstone bridge, the output of which was monitored on a potentimetric recorder [4]. A flexible probe (No. 402,

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Yellow Springs Instrument Co.), inserted 8 cm into the rectum, measured rectal temperature (T_{RE}). Leg (T_{LEG}) and tail (T_{TAIL}) temperatures were measured with surface temperature probes (No. 409, Yellow Springs Instrument Co.) affixed to the outer thigh and 3–4 cm distal to the base of the tail. Hypothalamic temperature ($T_{PO/AH}$) was measured with a thermistor (No. 32A7, Victory Engineering Co.) affixed to the tip of one of the thermodes.

Behavioral apparatus. Testing took place at approximately the same time of day in a temperature-controlled chamber maintained at 5 ± 1°C. Each monkey was restrained only during testing in a Plexiglas primate chair [4]. Pulling a Plexiglas rod suspended within reach of the monkey activated programming equipment, which turned on for 10 sec two pairs of quartz heat lamps (88 mw/cm^2) located to each side of the monkey. Behavioral responses were recorded with a digital counter, which printed cumulative totals at 10-min intervals.

Procedure

The procedure for training the monkeys to pull the rod for the radiant heat reinforcements has been described previously [4]. Following training, the monkeys were implanted, under sterile surgical procedures, with the thermode/cannula assembly. Details of the hypothalamic microinjection technique that was followed have also been described previously [6]. Norepinephrine (1-arterenol bitartrate, Sigma Chemical Co.) was dissolved in a sterile electrolyte solution (Normosol-R, pH 7.4, Abbot Laboratories). Doses of NE were calculated as the salt and refer to the concentration per μl. Injections were bilateral in a 1.0 μl volume. Control injections consisted of bilateral injections of 1.0 μl Normosol-R.

Preoptic and anterior hypothalamic temperature was altered by allowing temperature-controlled water to flow through the thermodes [4]. The actual change in local temperature at the rostral injection site during experimental changes in $T_{PO/AH}$ was slightly less than that measured by the thermistor due to the presence of thermal gradients surrounding the thermodes [4]. At the beginning of an experiment, 60–90 min was allowed for the monkey to establish stable temperatures and behavioral response rate at the cold T_A; $T_{PO/AH}$ was then displaced for 60 min. After a 40–45 min recovery period following the termination of the displacement of $T_{PO/AH}$, the microinjection cannulae were inserted into the cannula guides. After an additional 15–20 min, $T_{PO/AH}$ was displaced to the same level, and 30 min later a control or NE solution was injected from outside the chamber without disturbing the monkey. At the end of one hour, $T_{PO/AH}$ was allowed to return to body temperature. The cannulae remained in place until the end of the test. Norepinephrine was injected during PO/AH cooling (32–34°C) and warming (40–42°C) in doses ranging from 5.0–20.0 μg.

RESULTS AND DISCUSSION

Over a dosage range of 2.5–15.0 μg, PO/AH injections of NE in the squirrel monkey are followed by dose-dependent reductions in T_{RE} and behavioral responses for radiant heat in a cold environment [5]. Under the conditions of the present study, it was found that injections of NE were always followed by reductions in T_{RE}, T_{LEG}, and T_{TAIL} and a suppression of behavioral responses for radiant heat regardless of whether $T_{PO/AH}$ was experimentally raised or lowered. Experimental elevation of $T_{PO/AH}$ is associated with a fall in T_{RE}, T_{LEG}, and behavioral responses for radiant heat and an increase in T_{TAIL} [4]. If NE was injected into the PO/AH during experimental warming of this region, the reduction in core temperature produced by the elevation of $T_{PO/AH}$ was potentiated, as shown in Fig. 1. During this test when $T_{PO/AH}$ was raised to 42°C for 60 min, T_{TAIL} rose, T_{RE} fell, and behavioral responses for radiant heat decreased slightly toward the end of the period of thermal stimulation. When 10 μg of NE was injected during the second displacement of $T_{PO/AH}$, T_{RE} dropped precipitously as did T_{LEG} and T_{TAIL}. Behavioral response rate was suppressed 14% during the first 10 min interval following the injection when compared to the 10-min interval preceding the injection and remained suppressed 14% during the next 10-min interval. Occasionally PO/AH warming failed to unequivocally reduce behavioral responses for radiant heat as was evident during this test, but injections of NE were always effective in suppressing behavioral responses. Changes in T_{TAIL} are often considered as qualitative indicators of alterations in peripheral vasomotor tone [4,10]. Thus, Fig. 1 indicates that although NE potentiated the fall in T_{RE}, this was accompanied by an opposing autonomic response, vasoconstriction. If $T_{PO/AH}$ is experimentally reduced, T_{RE}, T_{LEG}, and behavioral responses for radiant heat increase, and T_{TAIL} may decrease [4]. The injection of NE during PO/AH cooling reversed the effects of lowering $T_{PO/AH}$, resulting in a return of T_{RE}, T_{LEG}, and behavioral response rate to precooling levels. As indicated in Fig. 2, the injection of 10 μg of NE when $T_{PO/AH}$ was lowered to 32.5°C was accompanied by a reduction in T_{RE}, T_{LEG}, and behavioral responses for radiant heat. Tail temperature showed little change. Control injections were without effect on core and peripheral temperatures and behavioral responses for radiant heat during PO/AH warming or cooling.

The magnitude of the effect of a single dose of NE seemed to be unaffected by changes in $T_{PO/AH}$. For Monkey C during the 10-min interval following an injection of 10 μg of NE, the mean changes in T_{RE} following each of two injections of NE during PO/AH cooling (32.5°C), PO/AH warming (42.0°C), and no displacement of $T_{PO/AH}$ were −0.48, −0.48, and −0.45°C, respectively. The mean changes in behavioral responses for radiant heat during the same interval were, respectively, −19.3, −18.2, and −21.2% for PO/AH cooling, PO/AH warming, and no displacement of $T_{PO/AH}$. Two other monkeys showed similar additive relationships between $T_{PO/AH}$ and injections of NE. Lack of repeated observations at each concentration of NE tested during concurrent PO/AH thermal stimulation precludes presenting a detailed dose-response analysis. In general as the concentration of NE was increased, the magnitude of the reduction in T_{RE} and behavioral response rate also increased irrespective of $T_{PO/AH}$.

Several behavioral outcomes may follow a drug treatment that alters thermal balance [9]. First, behavioral thermoregulatory responses might be insensitive to the change in body temperature and remain unchanged. Second, behavioral responses might compensate for the drug-induced change in temperature. Finally, behavior might be complementary so as to facilitate the change in body temperature. This latter outcome is consonant with the behavioral changes noted in the present study and also following NE injections in the absence of experimental

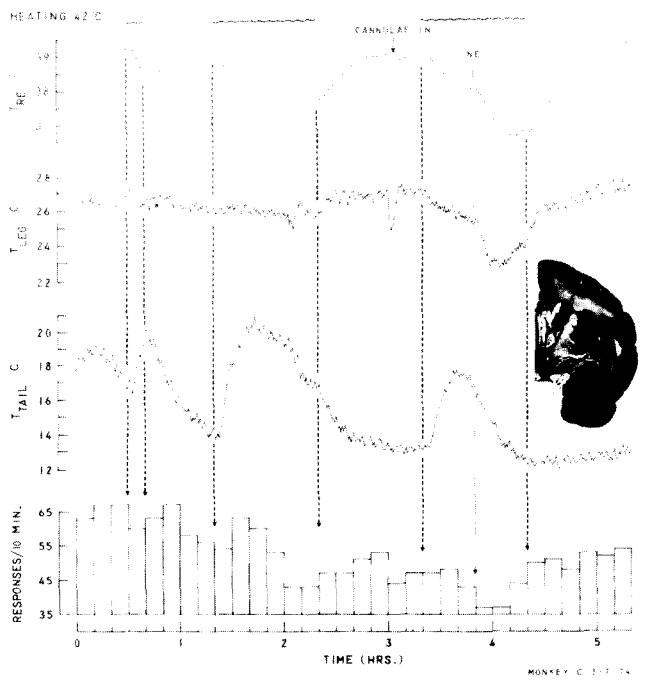

FIG. 1. The effect of a bilateral injection of 10 μg NE on temperature and behavioral response rate during PO/AH warming to 42°C in Monkey C. Periods of PO/AH warming are indicated by the wavy lines at the top of the figure and are enclosed by broken vertical lines. The first arrow indicates the insertion of the cannulae, and the second arrow indicates the injection of NE. Preoptic and anterior hypothalamic temperature was displaced briefly at the beginning of the test session to ensure that the thermodes were not occluded. Note the rapid rise in T_{TAIL} indicating peripheral vasodilation [4,10] during PO/AH warming and the fall in T_{TAIL} following the injection of NE. Inset on the right is a photomicrograph of a cresyl violet stained section of the microinjection site for Monkey C. The injection site on the contralateral side was at an equivalent location. The thermodes were located lateral to the anterior hypothalamus, approximately 1.0 mm dorsal to the optic chiasm, and approximately 1.0 mm posterior to this site [4]. Ambient temperature = 5 ± 1°C.

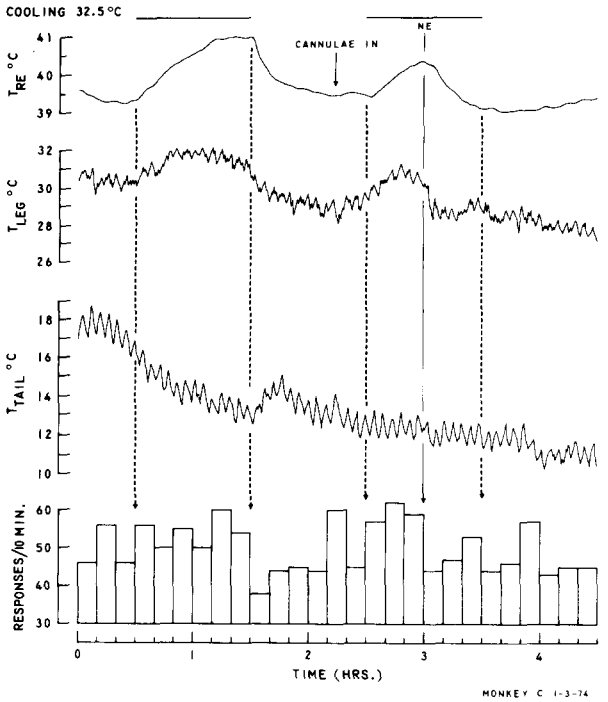

FIG. 2. The effect of a bilateral injection of 10 μg of NE on temperature and behavioral response rate during PO/AH cooling to 32.5°C in Monkey C. Periods of PO/AH cooling are indicated by the bars at the top of the figure and are enclosed by broken vertical lines. Cannulae insertion and injection of NE are indicated as in Fig. 1. The injection site was the same as shown in Fig. 1. Ambient temperature = 5 ± 1°C.

displacement of $T_{PO/AH}$ [5]. If a pharmacological agent lowers body temperature and autonomic and behavioral thermoregulatory responses facilitate that change in temperature, a reduction in the hypothalamic set point about which body temperature is regulated may be inferred [3, 6, 9]. In the present study, the fall in T_{RE} and behavioral response rate was often accompanied by the appearance of somnolent behavior including eye closure and reduced activity. A reduction in behavioral response rate may not necessarily represent the direct activation of heat loss, because a somnolent animal may have a diminished capacity to respond behaviorally. Thus if it is to be concluded that NE lowers the set point, it must also be demonstrated that NE activates heat-escape responses. The observation of a reduction in T_{TAIL}, indicating vasoconstriction, following NE injection implies that autonomic responses might be compensating for the reduction in body temperature. Opposing behavioral and autonomic responses are suggestive that NE has not altered set point mechanisms but may have instead acted nonspecifically on effector pathways. Finally, the failure of $T_{PO/AH}$ to alter the magnitude of the effect of NE on T_{RE} and behavioral responses is noteworthy, because it implies that two separate but additive systems, one temperature-sensitive and the other catecholamine-sensitive, were affected by the two procedures.

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