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Body Temperature Responses at Different Ambient Temperatures Following Injections of Prostaglandin E_1 and Noradrenaline into the Brain

W. L. VEALE[1]

Division of Medical Physiology, Faculty of Medicine, University of Calgary, Calgary, Alberta

AND

I. Q. WHISHAW

Department of Psychology, University of Lethbridge, Lethbridge, Alberta

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VEALE, W. L. AND I. Q. WHISHAW. *Body temperature responses at different ambient temperatures following injections of prostaglandin E_1 and noradrenaline into the brain.* PHARMAC. BIOCHEM. BEHAV. 4(2) 143–150, 1976. – Since prostaglandins of the E series have been implicated in the production of fever by pyrogens, we have applied them directly to the anterior-hypothalamic preoptic area of uunanesthetized rats at various ambient temperatures. In this paper we have determined accurately the region of the brain of the rat from which temperature responses can be produced by local injection. In addition we present evidence to suggest that the responses to local injections of PGE_1 are relatively unaffected by environmental temperatures, whereas those in response to injections of noradrenaline are influenced by ambient temperature. These results are discussed in light of similar findings with respect to the response to pyrogens in that it is relatively unaltered by ambient temperature. This work lends further support to the hypothesis that pyrogens act in the hypothalamus by releasing prostaglandins.

Temperature regulation Chemical stimulation of brain Prostaglandin fever Noradrenaline and thermoregulation Ambient temperatures

THE prostaglandins were introduced into the field of thermoregulation and fever in 1970 when Milton and Wendlandt [16] found that a febrile response was produced in unanesthetized cats following the injection of prostaglandin E_1 (PGE_1) into the third cerebral ventricle. Feldberg and Saxena [10] extended these observations to include the rabbit and rat. More recently, the anterior hypothalamic-preoptic area (AH/POA) has been identified as the region of the brain tissue which is most sensitive to local application of prostaglandin E_1 [25]. There is a growing body of evidence to support the suggestion by Feldberg, Milton and their colleagues (see [9]) that prostaglandins may be mediators in fever produced by a pyrogen. It is well known that prostaglandins are normal constituents of hypothalamic tissue [13, 14, 15] and their presence in the cerebro-spinal fluid (csf) is more pronounced during the development of a fever due to a pyrogen and less pronounced following reduction of the fever with an antipyretic [6].

In contrast to the monoamines, PGE_1 and leucocyte pyrogen produce fevers in all common laboratory species tested so far [24]. Consistent with the theory of prostaglandin release by pyrogens in the production of fever is the observation that anti-inflammatory and antipyretic substances inhibit the synthesis of prostaglandins in various tissues including brain [12,23]. Further, it has been demonstrated that the latency of the febrile response following central injections of PGE_1 is less than that observed following injection of leucocyte pyrogen into the same area [21,22]. Further, Stitt has shown that for the rabbit ambient temperature does not alter the magnitude of the response following microinjection of PGE_1 into the AH/POA. Similar observations have been made following both intravenous and central injections of leucocyte pyrogen into this same species [4].

Since Feldberg and Myers proposed their monoamine theory of thermoregulation [7,8], it has received support from a great deal of work in several different species.

[1]Send reprint requests to Dr. W. L. Veale, Division of Medical Physiology, The University of Calgary, 2920 - 24th Avenue N. W., Calgary, Alberta, T2N 1N4.

Ambient temperature has been established as an important influence upon the thermoregulatory response following central injections of the monoamines [3]. In the rat, Avery [1] and Avery and Penn [2] have shown that microinjections of cholinergic and adrenergic compounds into the AH/POA of the unanesthetized rat are influenced greatly by ambient temperature. For example, at a relatively neutral ambient temperature, local injections of noradrenaline (NA) produced a decrease in body temperature. At a hot ambient temperature, however, NA tended to defend against the naturally occurring increase in body temperature due to the high environmental temperature. In the cold, NA produced an increase in body temperature.

The experiments described in this paper were conducted to determine the changes in body temperature which occur in response to the direct application of PGE_1 and NA to various regions of the brain of the unanesthetized rat and to determine how the responses obtained are influenced by the ambient temperature. In addition to determining accurately the region of the brain from which temperature responses can be produced by local injection, we present evidence to suggest that the response to local injections of PGE_1 are relatively unaffected by environmental temperature whereas those in response to injections of NA are influenced by the ambient temperature.

METHOD

Animals

Experiments were performed with 54 male, Sprague-Dawley rats ranging in weight from 325–380 g. The rats were housed individually in constant light with free access to food and water throughout the experiments.

Procedure

Surgery. Each rat was anesthetized with pentobarbitone sodium injected intraperitoneally (40 mg/kg). Using standard stereotaxic procedures, two guide tubes were implanted bilaterally so that the tip of each was positioned 3 mm above the site of injection. Each guide tube was made from 20 ga stainless steel tubing and fitted with an indwelling stylet of corresponding length made from stainless steel. The guide tubes were fixed to the skull with stainless steel jeweler's screws and cranioplast cement. Postoperatively, penicillin was given intramuscularly for 3 days. Seven to 10 days elapsed before experiments were begun.

Injection placements. Sites selected for injection were based on the rat stereotaxic atlas of Pellegrino and Cushman [20]. Co-ordinates for injection sites were: anterior hypothalamus, anterior to bregma 2.0–2.4 mm, lateral to the midline 1.5 mm, and ventral from the dura 8.2 mm; lateral hypothalamus, 0.6 to −1.6 mm anterior, 1.5 mm lateral, 9.0 mm ventral; midbrain, −2.0 to −3.0 mm anterior, 1.5 mm lateral, 7.5 to 8.2 mm ventral; hippocampus, −2.0 and −3.2 mm anterior, 2.0 and 5.0 mm lateral, 3.5 and 8.5 mm ventral; amygdala, −1.0 mm anterior, 5.0 mm lateral and 9.0 mm ventral.

Injection procedure. Microinjections were made using 27 ga hypodermic tubing which was lowered through the guide tube so that its tip extended beyond the guide tube to the desired depth into the tissue to be stimulated. The injection cannula was connected to a length of PE 20 tubing; both were filled with and stored continuously in 70% ethyl alcohol solution which was then washed out thoroughly with sterile, pyrogen free saline before being filled with the solution to be injected. The PE tubing was attached to a 10 μl syringe mounted on a infusion pump. Injections of a volume of 0.5 μl were given over a 30 sec interval.

Both NA and PGE_1 were dissolved in a modified Krebs solution which was made from ion exchanged, glass-distilled water which was passed through a sterilized millipore filter (0.22 μ), and which contained: Na 143.0 mM; K 5.8 mM; Ca 2.6 mM; Cl 128.2 mM; glucose 5.6 mM; Mg 1.2 mM; SO_4 1.2 mM; H_2PO_4 1.2 mM; HCO_3 25.0 mM. This solution was shown to be pyrogen-free by independent assay. NA used in these experiments was the chloride salt and doses are expressed as this salt. The animals received injections of either modified Krebs solution, 0.1, 1.0, 5.0 or 50.0 ng of PGE_1, or 5 or 25 μg NA at each injection site. In some instances injections of PGE_2 were administered in the same concentrations and the temperature responses produced were the same as those which occurred following PGE_1.

The experiments were conducted in ambient temperatures of 5°C, 19°C and 35°C. The animals were brought to the experimental room in groups of 6–12 and adapted to room temperature for 1–2 hr. Temperatures were then recorded with a Tele-thermometer with a No. 402 probe inserted 6.5 cm into the rectum at 15 min intervals for 1 hr prior to and for 3 hr following each injection. Observations were also made with respect to the animal's changes in activity. Injections were given in a randomized order and a period of at least 48 hr elapsed between successive microinjections to any one animal.

Histological examination. At the conclusion of the experiments, the locus of each injection site was verified using standard histological techniques. Bromphenol blue (0.5 μl) was injected into each injection locus after the animal was anesthetized with pentobarbitone sodium. The animals were then perfused through the heart, first with a saline solution and then with a solution of 10% Formalin which contained 0.9% NaCl. Frozen sections were cut at 30 μ and then mounted and stained with thionin.

RESULTS

The results of the present experiments are summarized on the basis of the chemical injected, dosage and the location of injection.

Anterior Hypothalamus

A summary of the results obtained at an ambient temperature of 19°C following injections of PGE_1 and NA into the anterior hypothalamus is given in Fig. 1. In addition, the mean maximum changes in core temperature recorded within the first 30 min following microinjections are given in Table 1 along with the standard error associated with this change and the level of statistical significance obtained with student *t* tests. In Fig. 1 it can be seen that injections (Fig. 1, top) of PGE_1 produced a sharp rise in core temperature which reached a maximum extent within 15 min. The change in core temperature obtained with PGE_1 was dose dependent and as can be seen from Table 1, significant rises in temperature were obtained with concentrations as low as 0.1 ng. Injections of of Krebs solution also produced rises in core temperature but these increases were more gradual and smaller than those produced by PGE_1. In fact, the increases produced by the Krebs solution

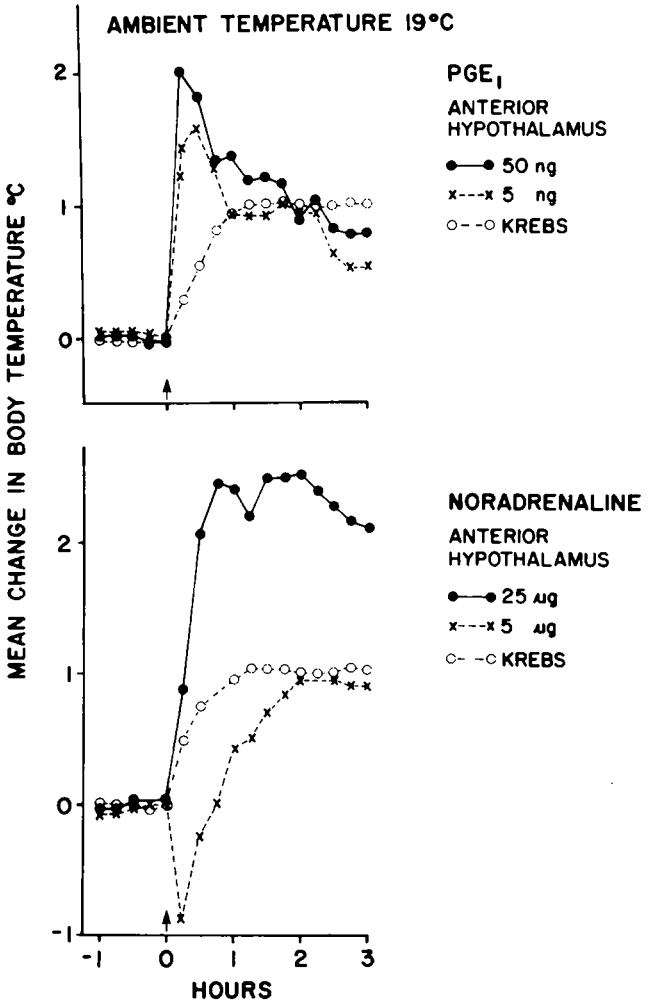

FIG. 1. (Top) Records of mean rectal temperatures obtained from unanesthetized rats at an ambient temperature of 19°C. At a time indicated by the arrow, 50 ng (•——•) PGE_1, 5 ng (×——×) PGE_1 or Krebs solution (○——○) was microinjected into the anterior hypothalamic area. (Bottom) Records of mean change in body temperature obtained from unanesthetized rats at an ambient temperature of 19°C. At the time indicated by the arrow, 25 µg NE (•——•), 5 µg NA (×——×) or Krebs solution (○——○) was injected into the anterior hypothalamic area.

did not reach a peak for about 1 hr following the injection whereas those due to PGE_1 were usually at their maximum in 15 min. In the series of experiments summarized in Fig. 1, the Krebs control solution was injected first. This injection was followed by the PGE_1 and NA and the final injection was also the Krebs solution. The second injection of the Krebs solution (Fig. 1, bottom) produced a response similar to that produced by the same solution injected (Fig. 1, top) several days and several injections earlier.

Injection of NA into the same anterior hypothalamic sites at which PGE_1 produced a rise in core temperature resulted in quite different effects (Fig. 1, bottom). Low doses of NA (5 µg) caused a fall in temperature which was both rapid and brief, occurring mainly within the first 15 min after the injection. Higher doses of Na (25 µg) produced a significant rise in core temperature which was less rapid but after about 45 min reached that obtained with PGE_1.

The behaviours associated with injections of different substances were also different. Following injections of PGE_1, the animals usually adopted a hunched posture, became piloerected, and particularly with higher dose, could be felt to shiver with light palpation. With lower doses of NA the animals adopted a prone posture for 10–20 min but with higher doses this posture was adopted for approximately 2–5 min. With the high dose of NA, the animals showed increased activity which was quite intense for 1–2 hr. The animals would stand on their hind feet with the front feet off the floor and if released from their cages would run around the room continuously, without attempting to hide or avoid recapture. When held, these animals seemed to have little muscle tone and remained quiet.

Lateral Hypothalamus

A summary of results obtained following injections of PGE_1 or NA into the lateral hypothalamic area is shown in Fig. 2. PGE_1 in a dose of 5 µg did not produce a significant change from baseline levels. The higher dose (50 µg) did produce an increase in body temperature which is statistically significant. As can be seen from Table 1, this increase in temperature was not as great as that following the injection of 0.1 µg PGE_1 in the AH/POA.

Injection of NA into the lateral hypothalamic area produced a dose dependent fall in core temperature with the response to the higher dose (25 µg) being statistically significant (Table 1). Following the lower dose of NA (5 µg), the animals adopted a prone posture for a period of 15–45 min. This type of behavior was more pronounced with the higher dose (25 µg), however, 3 animals with placements in the lateral hypothalamic-medial forebrain bundle area, curled up and adopted a sleeping posture immediately following microinjection. They continued to sleep for as long as 2 hr although they would jump up and turn or back up periodically. When these animals were held they showed a great deal of extensor rigidity and increased muscle tone.

Midbrain, Amygdala and Hippocampus

The temperature responses observed following PGE_1 and NA injected into the midbrain are shown in Fig. 3. As can be seen the higher dose of PGE_1 (50 ng) as well as the high dose of NA (25 µg) produced slight increases in body temperature but these changes are not statistically significant from baseline. As shown in Table 1, no statistically significant differences in temperature were produced by either PGE_1 or NA in the midbrain, amygdala or hippocampus. The statistical analysis were carried out using the maximum change in temperature within the first 30 min following the injection of the drug. As can be seen from Fig. 3, the higher dose of NA (25 µg) produced a delayed rise in body temperature but this increase was associated with a sharp increase in activity for as long as 2 hr. This increased activity included sniffing and rearing actions.

Effects of PGE_1 in Ambient Temperatures of 35°C and 5°C

A summary of the results obtained following the injection of PGE_1 into the AH/POA at ambient temperatures of 35°C and 5° is given in Fig. 4. PGE_1 produced rises in

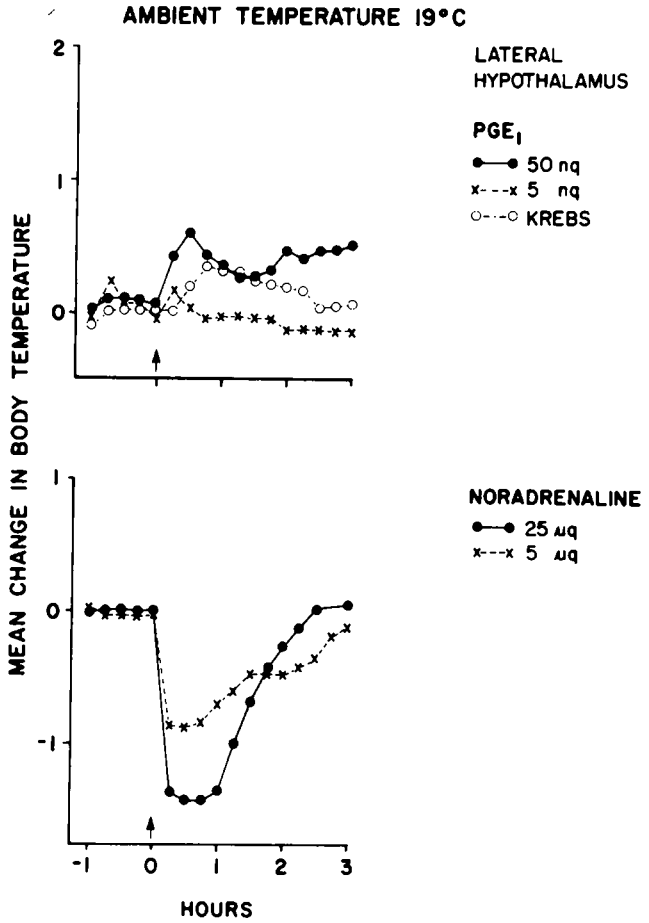

FIG. 2. (Top) Records of mean change in rectal temperature in unanesthetized rats at an ambient temperature of 19°C. At a time indicated by the arrow, 50 ng PGE_1 (●——●), 5 ng PGE_1 (×——×) or Krebs solution (○——○) was microinjected into the area of the lateral hypothalamus. (Botton) Mean change in rectal temperature for unanesthetized rats at 19°C. At a time indicated by the arrow 25 µg NA (●——●) or 5 µg noradrenaline (×——×) was injected into the region of the lateral hypothalamus.

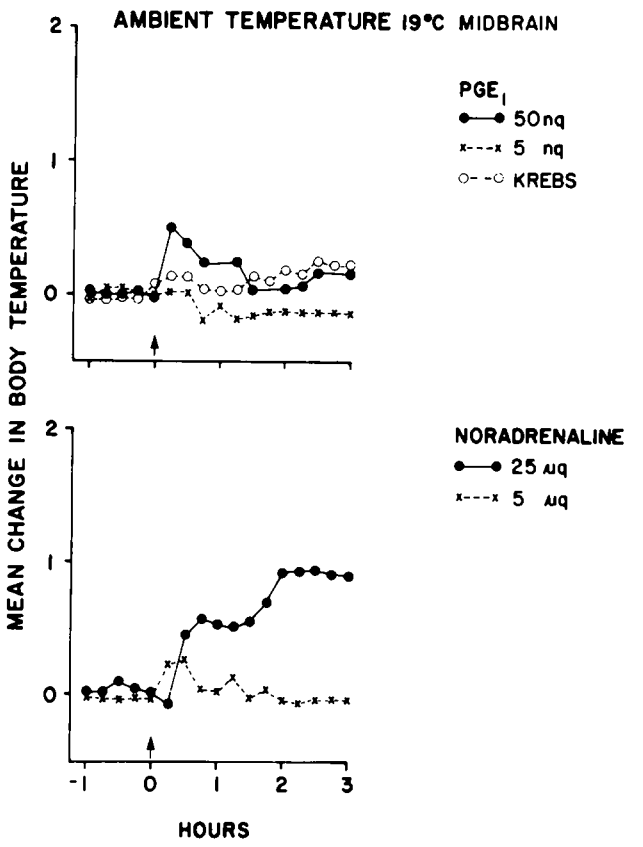

FIG. 3. Mean change in rectal temperature for unanesthetized rats at an ambient temperature of 19°C. (Top) At a time indicated by the arrow, 50 ng PGE_1 (●——●), 5 ng PGE_1 (×——×) or Krebs solution (○——○) was microinjected into the midbrain. (Bottom) At a time indicated by the arrow, 25 µg NA (×——×) was microinjected into the midbrain.

temperature similar to those seen at an ambient temperature of 19°C. The actual baseline temperature recorded when the animals were in an ambient temperature of 35°C was higher than in the ambient temperatures of 19°C and 5°C (39°C vs 38°C). This may account for the failure to observe a dose dependent temperature change following 5 ng and 50 ng PGE_1. The changes in core temperature with standard errors are summarized in Tables 2 and 3.

Effects of NA in Ambient Temperatures of 35°C and 5°C

A summary of the effects of NA treatments in ambient temperatures of 35°C and 5°C is given in Tables 2 and 3. It can be seen from Table 2 that injections of NA in the anterior hypothalamus in 35°C ambient temperature caused a statistically significant rise in core temperature in doses of 5 µg and 25 µg. The same treatments to rats in an ambient temperature of 5°C also caused rises in temperature, however, the increase with the low dose did not differ from control levels (Table 3).

Injection of NA in the lateral hypothalamus in 35°C ambient temperature caused a slight but significant decline with the lower dose (5 µg) and a significant increase with the higher dose (25 µg). In an ambient temperature of 5°C, NA caused a significant dose dependent decline which was greater for the high than for the low dose (Tables 2 and 3).

Injection of NA at both high and low dosage levels in midbrain sites did not produce temperature changes which differed significantly from control values in either ambient temperatures of 35°C or 5°C.

Histological Results

A summary of the sites of injection is given in Fig. 5. Placements in the anterior hypothalamus were found to be located in the preoptic anterior hypothalamic area ventral to the anterior commissure. Lateral hypothalamic placements were located in the lateral hypothalamic-medial forebrain bundle area from the caudal extent of the anterior hypothalamus to the level of the posterior hypothalamus. Midbrain placements can be seen to be located from the caudal extent of the posterior hypothalamus to the parafascicularis nucleus.

DISCUSSION

Results of this series of experiments indicated that, in the rat, prostaglandin E_1 best produces an increase in body

TABLE 1

MEAN VALUE AND STANDARD ERROR OF THE CHANGE IN BODY TEMPERATURE (°C) FROM BASELINE OF THE RAT WITHIN 30 MIN FOLLOWING MICROINJECTIONS OF PGE_1 AND NA IN DIFFERENT BRAIN SITES. THE EXPERIMENTS WERE CONDUCTED IN AN AMBIENT TEMPERATURE OF 19°C, THE NUMBER OF ANIMALS IS NOTED (N).

	N	Anterior Hypothalamus	Lateral Hypothalamus	Midbrain	Amygdala	Hippocampus
Control	6	+0.36 ± 0.16	+0.08 ± 0.15	+0.25 ± 0.13	+0.21 ± 0.08	+0.11 ± 0.12
NA (5 μg)	6	−0.96 ± 0.35†	−1.20 ± 0.38	+0.31 ± 0.14	+0.85 ± 0.20	+0.36 ± 0.26
NA (25 μg)	6	+1.75 ± 0.66*	−2.32 ±0.40‡	+0.48 ± 0.27	−0.20 ± 18	+0.46 ± 0.30
PGE_1 (0.1 ng)	6	+1.13 ± 0.18†	–	–	–	–
PGE_1 (1 ng)	6	+1.25 ± 0.12†	–	–	–	–
PGE_1 (5 ng)	6	+1.82 ± 0.16‡	−0.18 ± 16	+0.18 ± 0.25	+0.26 ± 0.05	+0.18 ± 0.15
PGE_1 (50 ng)	6	+2.30 ± 0.29‡	+0.85 ± 19‡	+0.60 ± 0.13	+0.50 ± 0.15	+0.45 ± 0.23

*<0.05 †<0.01 ‡<0.001

TABLE 2

MEAN VALUE AND STANDARD ERROR OF THE CHANGE IN BODY TEMPERATURE (°C) FROM BASELINE OF THE RAT WITHIN THE FIRST 30 MIN INTERVAL FOLLOWING MICROINJECTIONS OF PGE_1 AND NA IN DIFFERENT BRAIN SITES. THE EXPERIMENTS WERE CONDUCTED IN AN AMBIENT TEMPERATURE OF 5°C, THE NUMBER OF ANIMALS IS NOTED (N).

	N	Anterior Hypothalamus	Lateral Hypothalamus	Midbrain
Control	6	+0.45 ± 22	+0.30 ± 0.06	+0.48 ± 0.16
NA (5 μg)	6	+0.91 ± 0.30	−1.50 ± 0.35†	+0.38 ± 0.10
NA (25 μg)	6	+1.58 ± 0.50*	−2.45 ± 0.40†	+0.31 ± 0.19
PGE_1 (5 ng)	6	+1.13 ± 0.08*	–	–
PGE_1 (50 ng)	6	+1.75 ± 0.14†	–	–

*<0.05 †<0.001

temperature following its microinjection into the region of the anterior hypothalamus. This increase in dose dependent and appears to be relatively unrelated to the ambient temperature. The increases in body temperature due to local injection of PGE_1 into the AH/POA were approximately the same at the 3 ambient temperatures used, that is 35°C, 19°C and 5°C. The only other locus from which PGE_1 caused body temperature to increase significantly over baseline levels was when the higher dose (50 ng) was injected into the lateral hypothalamic area. Since the lower dose of prostaglandin at the same site did not cause body temperature to increase, the most probable explanation for the rise is that there is a diffusion from the lateral region of the hypothalamus to the anterior preoptic region. This is understandable since in the rat brain this distance is relatively short.

The temperature responses observed following the local injection of noradrenaline were dependent upon the site of injection, the amount injected and the ambient temperature. Our results essentially support those of Avery [1] and lend a further backing to the concepts put forth by Myers and Yaksh [18,19]. Noradrenaline injected into the AH/POA at an ambient temperature of 19°C caused an increase in body temperature with a higher dose and an

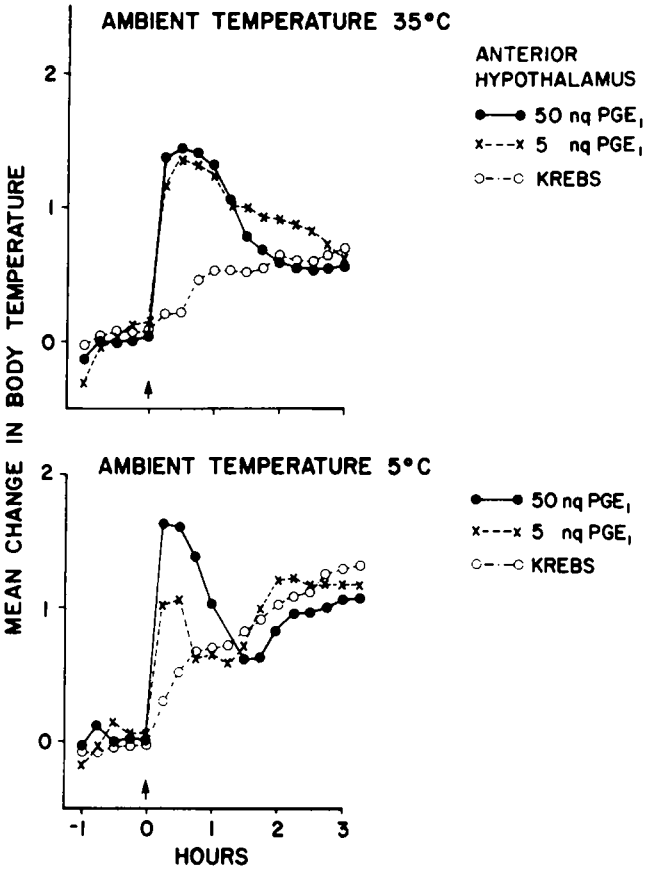

FIG. 4. (Top) Mean change in rectal temperature for unanesthetized rats at an ambient temperature of 35°C. At a time indicated by the arrow, 50 ng PGE_1 (●——●), 5 ng PGE_1 (x——x) or Krebs solution (○——○) was microinjected into the region of the anterior hypothalamus. (Bottom) Mean change in rectal temperature for unanesthetized rats at an ambient temperature of 5°C. At a time indicated by the arrow, 50 ng PGE_1 (●——●), 5 ng PGE_1 (x——x) or Krebs solution (○——○) was injected into the region of the anterior hypothalamus.

initial decrease in body temperature followed by an increase with the lower dose. At both 35°C and 5°C noradrenaline produced an increase in body temperature. At 19°C noradrenaline in the lateral hypothalamus produced a decrease in body temperature but had little or no effect on the midbrain, amygdala and hippocampus. At an ambient temperature of 35°C the higher dose of noradrenaline produced an increase in body temperature in the lateral hypothalamus whereas at the 5°C both doses of noradrenaline produced a fall. No consistent changes in body temperature was seen following injections of noradrenaline into the midbrain.

When injections of the modified Krebs vehicle were made into the anterior hypothalamus, increases in body temperature of as much as 1°C were observed. To test the vehicle for pyrogenicity a cross over assay was done on a group of rabbits. No pyrogenicity was detected in the injection solutions. The increases seen following injections into the anterior AH/POA were of a longer latency, more gradual and of smaller magnitude than the increases seen following injections of either noradrenaline or prostaglandin E_1. This type of increase is similar to that seen in other species following injection into or perfusion of the ventricular spaces or of the AH/POA [11,17]. This increase was not seen in other regions of the brain. Since body temperature was recorded every 15 min, the baseline temperatures varied considerably, and therefore, the data is expressed as the mean change from baseline temperature. The observation that the temperature response following injections of leucocyte pyrogen appeared to be unrelated to ambient temperature lends support to the concept that prostaglandin may be released by leucocyte pyrogen and that it may be a mediator in fever.

We have recently suggested that fever may represent a pathological state which involves prostaglandin and which may be superimposed upon normal thermoregulation [5]. Certainly the type of response seen with prostaglandin is similar to that seen for leucocyte pyrogen and this has been observed in other species as well [21,22]. As was observed by Stitt [21] in the rabbit the latency for febrile response following injection of the PGE_1 into the AH/POA was very

TABLE 3

MEAN VALUE AND STANDARD ERROR OF THE CHANGE IN BODY TEMPERATURE FROM BASELINE OF THE RAT WITHIN THE FIRST 30 MIN INTERVAL FOLLOWING MICROINJECTIONS OF PGE_1 AND NA IN DIFFERENT BRAIN SITES. THE EXPERIMENTS WERE CONDUCTED IN AN AMBIENT TEMPERATURE OF 35°C, THE NUMBER OF ANIMALS IS NOTED (N).

	N	Anterior Hypothalamus	Lateral Hypothalamus	Midbrain
Control	6	+0.05 ± 0.04	+0.30 ± 0.10	+0.06 ± 0.11
NA (5 μg)	6	+0.80 ± 0.16†	-0.13 ± 0.16*	+0.15 ± 0.10
NA (25 μg)	6	+0.86 ± 0.08‡	+0.81 ± 0.10‡	+0.35 ± 19
PGE_1 (5 ng)	6	+1.12 ± 0.12‡	–	
PGE_1 (50 ng)	6	+1.35 ± 0 09‡	–	

*<0.05 †<0.01 ‡<0.001

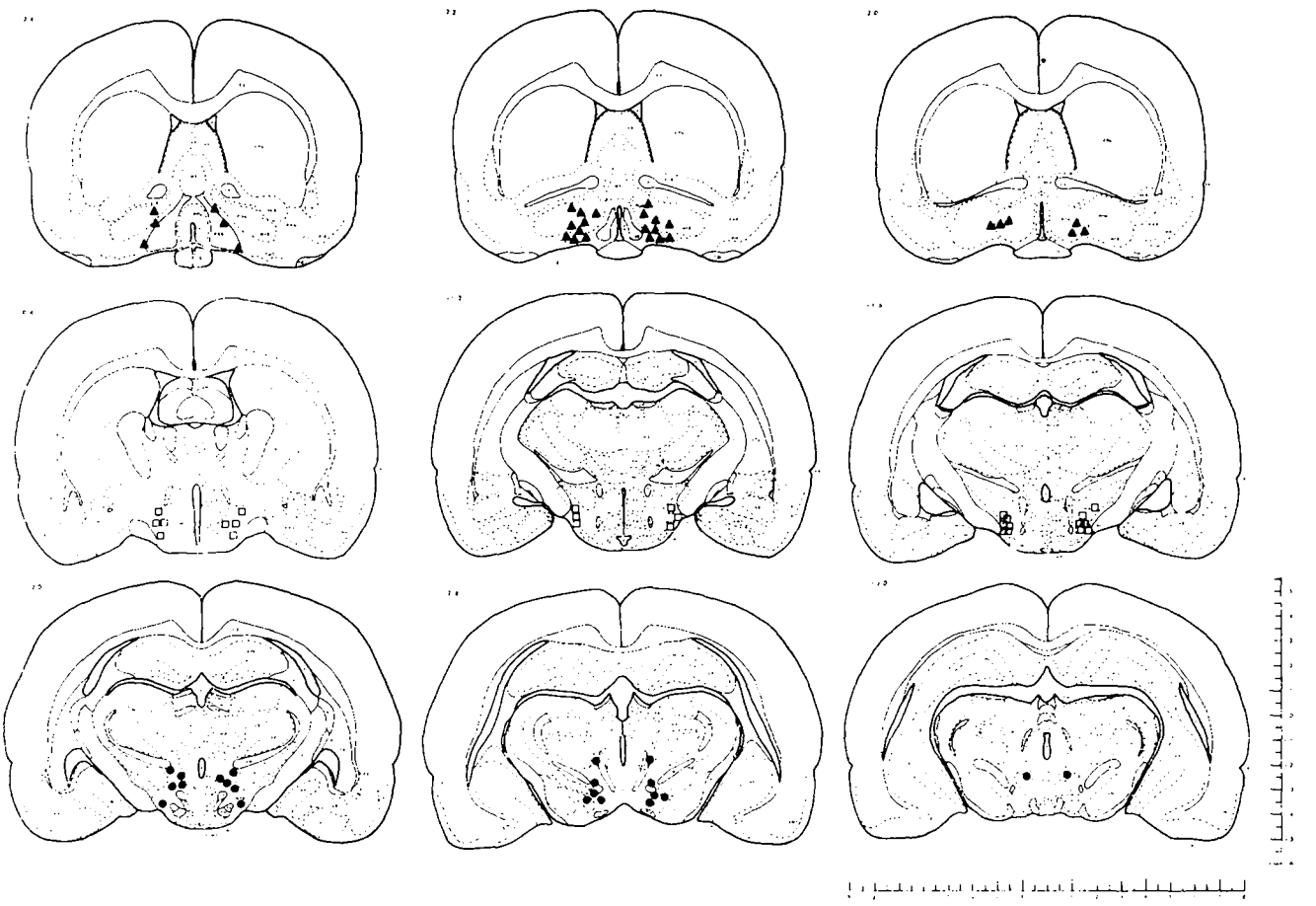

FIG. 5. A summary of loci of microinjections made in the anterior hypothalamic preoptic area are indicated by the solid triangles (top row). Injection sites in the region of the lateral hypothalamus are indicated by the open squares (middle row) and those for injections in the region of the posterior hypothalamus are indicated by the solid dots (bottom row).

short indeed, and in fact, shorter than that seen following local injections of leucocyte pyrogen [21,24].

Examination of the brains revealed that it is the AH/POA which is most sensitive to the injections of prostaglandin E_1 and a dose as small as 100 pg produced an increase in body temperature from this area. This is the same region of the brain from which leucocyte pyrogen best produces its febrile response in other species [24]. We interpret the results of these experiments as being consistent with the hypothesis put forth by Feldberg and Milton and their colleagues [9, 10, 16] that leucocyte pyrogen acts within the hypothalamus by releasing prostaglandins.

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