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FURTHER STUDIES ON PROSTAGLANDIN E_1 FEVER IN CATS

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SUMMARY

1. Micro-injections of a few nanograms of prostaglandin E_1 (PGE_1) into the anterior hypothalamus of unanaesthetized cats produced a rise in rectal temperature, whereas temperature was not affected when micro-injections of even larger doses were made into the posterior hypothalamus. The hyperthermia produced by injections of PGE_1 into the cerebral ventricles is therefore attributed to an action of PGE_1 on the anterior hypothalamus.

2. During a pentobarbitone sodium anaesthesia the sensitivity of cats to the hyperthermic effect of PGE_1 injected into the cerebral ventricles was found to be greatly reduced, particularly during the early stage of anaesthesia when body temperature was falling steeply.

INTRODUCTION

Recently it was shown (Milton & Wendlandt, 1970; Feldberg & Saxena, 1971*a*) that prostaglandin E_1 (PGE_1) produces hyperthermia when injected in minute amounts into the cerebral ventricles of unanaesthetized cats, rabbits, or rats. The site of action was not determined, but the anterior hypothalamus, particularly its rostral part, the pre-optic area, was suggested as the most likely site, since the monoamines as well as leucocyte pyrogen act on this region when affecting body temperature. On the other hand, the posterior hypothalamus where acetylcholine acts when producing its hyperthermic effect in monkeys (Myers & Yaksh, 1969), was not excluded as an alternative site.

In the present experiments, micro-injections of PGE_1 were made into the hypothalamus in unanaesthetized cats. Hyperthermia occurred only when the PGE_1 was injected into the anterior, not when injected into the posterior hypothalamus. In addition, it was found, also in cats, that the sensitivity to the hyperthermic effect of PGE_1 injected intraventricularly was greatly diminished in pentobarbitone sodium anaesthesia.

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METHODS

The experiments were done on cats of both sexes weighing between 2·5 and 3·5 kg. In an aseptic operation under pentobarbitone sodium anaesthesia, a Collison cannula was implanted either into the hypothalamus for micro-injections, or into the left lateral ventricle for intraventricular injections.

The Collison cannula used for micro-injections had a 22 mm long shaft consisting of stainless-steel tubing (22 gauge) with an indwelling stilette. It was implanted stereotaxically. The co-ordinates, taken from the atlas of Snider & Niemer (1961), were 1 to 1·5 mm lateral to the mid-line, 6·5–7·5 mm above the interaural zero line and, when the injections were to be made into the anterior hypothalamus, 12–14 mm, when into the posterior hypothalamus, 9 mm anterior to the interaural plane. The cannula was fixed to the skull with acrylic cement. After recovery from the operation, injections were made without anaesthesia once or twice a week. For the injections, the cat was removed from its cage, the cap of the cannula and the stilette was removed and a stainless-steel tube (28 gauge) connected by polyethylene tubing to a 10 μl. Hamilton syringe, was inserted 1 mm beyond the end of the outer guide cannula. Before insertion, cannula and polythene tubing were filled with the solution to be injected, whereas the syringe was filled with absolute alcohol. The syringe was driven by a specially constructed pump which delivered 1 μl. (the volume to be injected) per min. The inner cannula was left inserted for 30 sec after the end of the injection, it was then replaced by the stilette, the cap was screwed on, and the cat returned to its cage.

The procedures used for implantation of the Collison cannula into the left lateral ventricle and for the subsequent intraventricular injections were the same as described in detail elsewhere (Feldberg & Saxena, 1971*b*).

Rectal temperature was recorded at room temperature (19 to 23° C) with a thermister probe (Yellow Spring Instrument Co.) inserted about 10 cm into the rectum and held in position by adhesive tape which was attached to its protruding end and gently wrapped around the base of the tail. Temperature was monitored continuously by a Kent multichannel recorder, and the figures given in this paper were plotted directly from the tracings obtained in this way. During recording of the temperature, the cats were allowed to move freely in their cages.

The PGE_1, 100 μg/ml., was dissolved in a 0·9 % NaCl solution and the solution was kept frozen until used; dilutions were made with the artificial c.s.f. of Merlis (1940). The noradrenaline used was the hydrochloride and the values given in the text refer to the salt. All solutions, glassware, syringes and tubing used for the injections were sterile; the solutions and glassware were pyrogen-free as well.

RESULTS

Micro-injections into the anterior and posterior hypothalamus

Fig. 1 gives typical results obtained with micro-injections of PGE_1 into the anterior hypothalamus. The three records on the left and the upper record on the right, were from the same cat obtained on different days. Fig. 2 gives a frontal section of the brain from this cat. It shows the entire needle tract made by the micro-injection cannula which ends in the rostral part of the anterior hypothalamus.

In several cats the procedure involved in the micro-injection itself

produced a small, short lasting rise in temperature, probably emotional in origin. It did not happen in this cat, and a micro-injection of 1 μl. artificial c.s.f. had no effect on temperature, whereas a small but definite

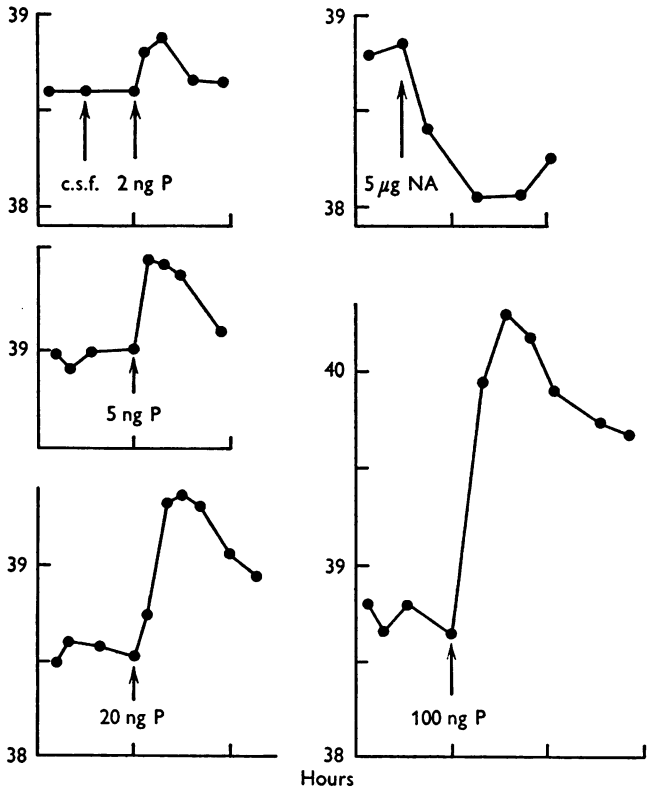

Fig. 1. Records of rectal temperature obtained from two unanaesthetized cats, each with an indwelling micro-injection cannula in the left anterior hypothalamus (site of injection: 1·5 mm lateral to mid line; 13·5 mm anterior to and 6·5 mm above interaural zero line of Snider & Niemer, 1961). Left records and upper right record obtained from same cat on different days. Each arrow indicates a micro-injection of 1 μl. fluid of artificial c.s.f. or of artificial c.s.f. containing 2, 5, 10, or 100 ng PGE_1 (P), or 5 μg noradrenaline (NA).

rise was obtained with as little as 2 ng PGE_1. These results are shown in the top left record, whereas the middle and bottom left records show the greater and longer lasting rises produced by 5 and 20 ng PGE_1. A micro-injection of 5 μg noradrenaline into the same region produced its typical hypothermic response, as shown in the top right record. The large rise of over 1·5° C shown in the bottom right record was obtained in another cat

with 100 ng PGE_1. The micro-injection cannula was inserted at the same point, 13·5 mm anterior to the interaural plane, and frontal sections of the brain showed the needle tract to be in the same position as shown in Fig. 2. In other cats in which the micro-injection cannula was inserted a little

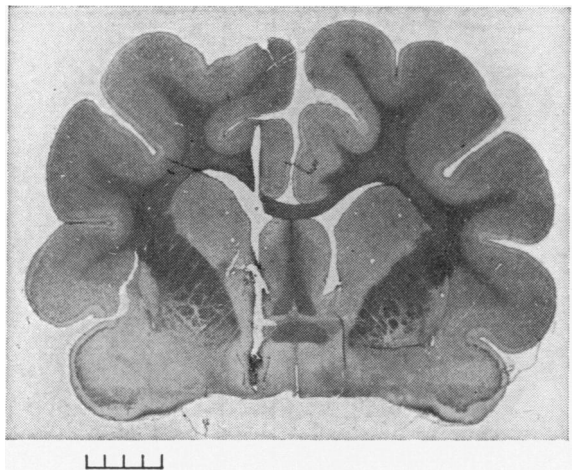

Fig. 2. Frontal section of the brain of the cat from which the records on the left and the upper right record of Fig. 1 were obtained. The section shows needle tract ending in the region of the anterior hypothalamus, and made by the Collison cannula implanted 1·5 mm lateral to the mid line and 13·5 mm anterior to and 6·5 mm above the interaural zero line of Snider & Niemer (1961). Each division of scale shown at the bottom corresponds to 1 mm.

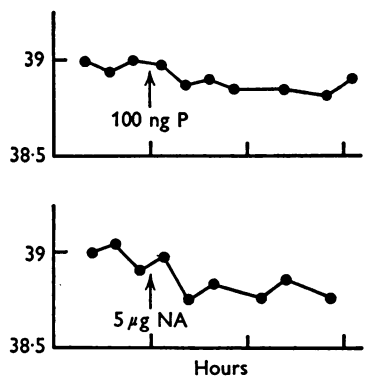

Fig. 3. Records of rectal temperature obtained on different days from an unanaesthetized cat with indwelling micro-injection cannula in the left posterior hypothalamus (site of injection: 1 mm lateral to mid line, 9 mm anterior to and 6 mm above the interaural zero line of Snider & Niemen, 1961). At the arrow, micro-injection of 100 ng PGE_1 (upper record) and of 5 μg noradrenaline (lower record).

more rostral, i.e. 14 mm, or a little more caudal, i.e. 13 or 12 mm anterior to the interaural plane, the results were the same.

When the injections were repeated on different days, the effect of PGE_1, but not that of noradrenaline, usually became much smaller, and the threshold for PGE_1 was raised, but by lowering the inner cannula by another millimeter the response was restored.

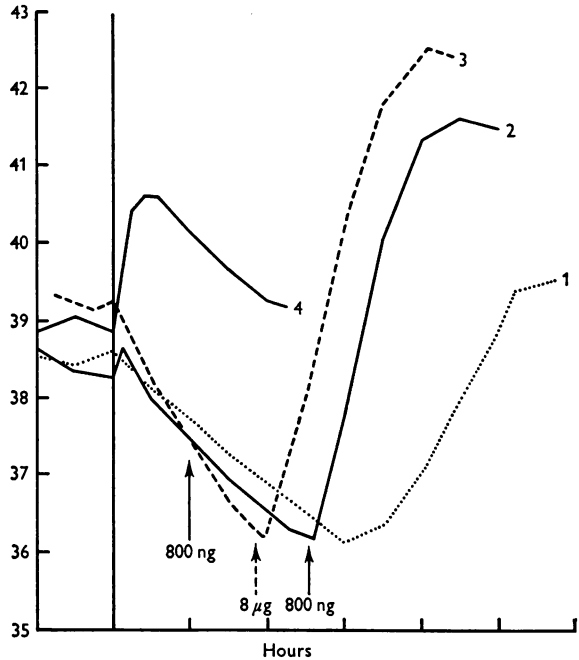

Fig. 4. Records of rectal temperature obtained on different days from the same cat. The vertical line at 1 hr indicates an intraperitoneal injection of pentobarbitone sodium, 36 mg/kg, for record 1, 2 and 3, and an intraventricular injection of 800 ng PGE_1 for record 4. Intraventricular injections of 800 ng PGE_1 referring to record 2, are indicated by the continuous arrows (↑), whereas the interrupted arrow (⇡) refers to record 3 and indicates an intraventricular injection of 8 μg PGE_1.

Fig. 3 shows the different result when the PGE_1 was injected into the posterior hypothalamus. Neither PGE_1 in a dose of 100 ng (upper record) nor noradrenaline in a dose of 5 μg injected into the same site a few days later (lower record) had a definite effect on temperature. In some similar experiments on other cats in which the micro-injections of PGE_1 were ineffective, those of noradrenaline produced a small but definite fall in temperature. This suggests that the area on which noradrenaline acts when lowering temperature is more extensive than the one on which PGE_1 acts when raising temperature.

Intraventricular injections during pentobarbitone sodium anaesthesia

During pentobarbitone sodium anaesthesia, particularly during its initial stage when temperature is falling, the sensitivity to an intraventricular injection of PGE_1 is greatly reduced. In the unanaesthetized cat, as little as 20 or even 10 ng is often sufficient to produce a small rise in temperature when injected intraventricularly, and ten times larger doses regularly produce an appreciable rise. During the first 1–1½ hr of a pentobarbitone sodium anaesthesia, however, whilst temperature is falling, even 800 ng is ineffective and does not interrupt the fall. At a later stage, when the fall in temperature produced by the anaesthetic has nearly come to an end, the same dose becomes effective. Temperature begins to rise within a few minutes of the injection and rises beyond the level it would attain without the injection. Temperature rises even higher than the level reached by the same dose of PGE_1 given to the non-anaesthetized cat. These findings are illustrated in Fig. 4. Record 1 shows the fall and return of temperature produced by the anaesthetic alone. Record 2 shows the effects of two intraventricular injections of 800 ng. The first one, given 1 hr after initiation of the anaesthesia at a time when temperature was still falling steeply, did not affect the fall, whereas temperature began to rise a few minutes after the second injection, given 1·5 hr later, and rose to 41·6° C. This is 2·1° C higher than the level to which temperature returned in record 1, and 1° C higher than the level reached in the unanaesthetized cat by an intraventricular injection of 800 ng PGE_1, which, as shown in record 4, caused temperature to rise from 33·8 to 40·6° C. With doses greater than 800 ng, the PGE_1 became effective at a somewhat earlier stage of the anaesthesia and temperature rose to even higher levels. For instance, record 3 shows a rise of 6° C in 1 hr, to 42·5° C in response to 8 μg PGE_1 which was injected intraventricularly 110 min after anaesthesia was initiated by intraperitoneal pentobarbitone sodium.

DISCUSSION

From the results obtained with micro-injections of PGE_1 into different parts of the hypothalamus of cats, it is evident that the site where PGE_1 acts when producing its hyperthermic effect on injection into the cerebral ventricles is the same as that on which the monoamines and pyrogen act when affecting temperature, i.e. the anterior and not the posterior hypothalamus. The site where noradrenaline acts when lowering temperature may, however, be a little more extensive.

At present nothing definite is known about a physiological role of PGE_1 in temperature regulation. Yet the finding that it raises temperature when

injected in minute amounts, that is, in nanograms, into the anterior hypothalamus, combined with the fact that PGE_1 is a natural constituent of the hypothalamus, and can be detected in c.s.f. as well as in the effluent during perfusion of the cerebral ventricles, points to the possibility that by its continuous release it plays a role in maintaining body temperature. In that case, the hypothermia of anaesthesia could, at least in part, result from an insensitivity of the anterior hypothalamus to PGE_1 brought about by the anaesthetic. It has been shown that the hypothermia of anaesthesia results from an action of the anaesthetics on the hypothalamus (Feldberg & Myers, 1964), and in the present experiments it was found that during a pentobarbitone sodium anaesthesia, particularly during its early stage, when temperature was falling steeply, PGE_1 injected intraventricularly in a dose many times greater than that required to raise temperature in the non-anaesthetized cat, did not affect temperature. When the fall in temperature produced by the pentobarbitone sodium came to an end, i.e. shortly before temperature began to return to normal, the sensitivity to PGE_1 also began to return.

Previously the fall during anaesthesia had been explained on the assumption that the anaesthetics increase the release of the monoamines in the hypothalamus and that the hypothermic effect of the released noradrenaline is more effective than the hyperthermic effect of the released 5-HT. At present both possibilities which are not exclusive have to be kept in mind because there is as yet no evidence that anaesthetics increase the release of the monoamines or that body temperature is maintained by a continuous release of PGE_1 in the hypothalamus.

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