Br. J. Pharmac. Chemother. (1968), **32**, 523–538.

EFFECT ON BODY TEMPERATURE OF MORPHINE AND ERGOTAMINE INJECTED INTO THE CEREBRAL VENTRICLES OF CATS

BY

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(*Received October* 13, 1967)

Morphine and ergotamine have been examined in cats to find out how they affect body temperature when acting on the hypothalamus. The two substances were chosen to investigate whether a substance such as morphine, which reduces the monoamines in the hypothalamus, affects body temperature when injected into the cerebral ventricles, and whether a substance such as ergotamine, which blocks the action of the monoamines in peripheral tissues, exerts this effect also on the anterior hypothalamus.

A reduction by morphine of the noradrenaline and adrenaline content of the hypothalamus and brain stem has been observed in all species examined, and this effect is prevented by nalorphine (Vogt, 1954 ; Holzbauer & Vogt, 1954 ; Gunne, 1959 ; Maynert & Klingman, 1962 ; Maynert & Levi, 1965). In cats morphine also reduces diencephalic 5-hydroxytryptamine (5-HT) (Turker & Akcasa, 1962), but this has not been observed in dogs and rabbits (Maynert, Klingman & Kaji, 1962). On the other hand, release of 5-HT by morphine from tissues other than the brain has been obtained in perfusion experiments from hind quarters of rats (Bhattacharya & Lewis, 1956) and from intestinal preparations of dogs (Burks & Long, 1967).

If morphine were to affect body temperature by release of hypothalamic monoamines, its effect should vary in different species because the monoamines affect temperature differently in different species when acting on the hypothalamus. Injected systemically, the effect of morphine varies not only in different species but also in different conditions, because hypo and hyperthermia have been obtained in the same species (for references see Eichenberger, 1966). It is difficult to draw definite conclusions about the site of action of morphine from these results obtained on systemic application, because they may result from a combination of a variety of effects. To study the effects of morphine on the anterior hypothalamus, however, two methods are available. The morphine may either be injected into this part of the brain or introduced into the cerebral ventricles.

On rats, Lotti, Lomax & George (1965) have found that microinjections into the anterior hypothalamus of rats produced pronounced hypothermia. On cats, Gaddum & Vogt (1956) as well as Borison, Fishburn, Bhide & McCarthy (1962) have injected

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† Supported by U.S. Public Health Service Fellowship No. 1-F2-GM-22, 826-02, from the National Institute of General Medical Sciences.

morphine into the cerebral ventricles but the experiments were done without recording body temperature. Such injections were found by Gaddum & Vogt (1956) to produce strong excitation in the unanaesthetized cat, which would interfere with temperature responses caused by an action on the hypothalamus. In the present experiments morphine was therefore either injected into the cerebral ventricles or perfused through the third ventricle in animals anaesthetized with pentobarbitone sodium. In these experiments morphine had the opposite effect from that in rats; it produced a rise in temperature. The effect was antagonized by the specific morphine antagonist nalorphine.

The adrenaline blocking effect of ergot alkaloids on peripheral tissues was discovered more than 60 years ago by Dale (1906). These alkaloids block or reverse the pressor effects on the arterial blood pressure of adrenaline and other sympathomimetic amines, as well as of sympathetic nerve stimulation. The present experiments show that ergotamine has this action also on the hypothalamus when injected into the cerebral ventricles, and that the hypothalamus becomes insensitive not only to the temperature effects of the catecholamines, but also to those of 5-HT, morphine and pentobarbitone sodium.

The paper includes experiments on the effects on temperature produced by fixing the head to the ear bars and mouthpiece of a stereotaxic instrument, and by cannulating a lateral ventricle.

METHODS

The experiments were carried out on cats of either sex weighing between 2.5 and 3.8 kg.

For the injection of drugs into the cerebral ventricles a Collison cannula was aseptically implanted under pentobarbitone sodium anaesthesia into a lateral ventricle, as originally described by Feldberg & Sherwood (1953) with the modifications given by Carmichael, Feldberg & Fleischhauer (1964). The point of insertion of the cannula on the skull was 12 mm in front of the interaural plane and 3 mm lateral to the midline. The shaft of the cannula was 12.5 mm long and the side opening near the tip when facing medially was opposite the foramen of Monro. Injections were made after an interval of at least 4 days after the implantation. Each drug was injected in a volume of 0.1 ml., and washed in by 0.05 ml., of 0.9% NaCl solution. For perfusion of the cerebral ventricles, either from the left lateral or from the third ventricle to aqueduct, the method used was that described by Feldberg & Fleischauer (1962) with the modifications given by Carmichael *et al.* (1964). The perfusion fluid was the artificial cerebrospinal fluid of Merlis (1940).

Rectal temperature was recorded by a thermistor probe inserted 8–10 cm into the rectum and affixed with adhesive tape to the root of the tail. Temperature was monitored continuously by a Kent multi-channel recorder. The figures reproduced in this paper are plotted directly from the tracings obtained in this way.

Drugs

The drugs used were: morphine sulphate; nalorphine hydrobromide (Lethidrone, Burroughs Wellcome & Co.); adrenaline and noradrenaline bitartrate; ergotamine tartrate (Sandoz). The doses refer to the salts.

RESULTS

Fixing the head to the stereotaxic instrument and cannulation of a lateral ventricle

Fixing the head of a cat anaesthetized with intraperitoneal pentobarbitone sodium to the ear bars and mouthpiece of a stereotaxic instrument and implanting a cannula into

a lateral ventricle results in shivering, constriction of the ear vessels and a rise in rectal temperature.

The rise in temperature is shown in Fig. 1A. The interrupted curve was obtained during anaesthesia alone. Temperature continued to fall for more than 3 hr to 34.5° C and then rose to 39.5° C during the following 2 hr while the cat was shivering. The continuous curve with solid circles was obtained 4 days later. The head was fixed to the stereotaxic instrument 40 min after the pentobarbitone sodium injection and a Collison cannula implanted into the left lateral ventricle; the fall in temperature was arrested within a few minutes although temperature was still above 36° C; the cat began to shiver and temperature rose to 40.9° C during the following 3 hr and remained at nearly this level (40.5° C) for at least another 2 hr.

The cannulation of the lateral ventricle was only partly responsible for the observed rise in temperature. Implanting a sham cannula into the skull which did not penetrate the dura, or only fixing the head to the stereotaxic instrument caused a rise which, however, was not as great and not as long-lasting as that obtained on cannulation of a lateral ventricle.

The effect of fixing the head to the stereotaxic instrument for 30 min is shown by the curve with the open circles in Fig. 1A. During the first minutes temperature fell more steeply, an effect observed in other experiments as well, but then the cat shivered and temperature began to rise, that is, temperature rose earlier than under pentobarbitone sodium alone but it did not rise higher. After 2 hr the rise was interrupted by a fall which may indicate that the temperature response to the stimulus of fixing the head had ceased.

The temperature curves of Fig. 1B were obtained from another cat. The interrupted curve again shows the effect of the pentobarbitone sodium anaesthesia alone, and the curve with the open circles the effect of sham cannulation. Shortly after fixing the head to the stereotaxic instrument, even before implantation of the sham cannula, the cat began to shiver and the fall in temperature was arrested. Subsequently temperature rose to 40.4° C. The curve with the solid circles shows the effect produced by replacing the sham cannula with a Collison cannula but without fixing the head to the stereotaxic instrument. Temperature continued to fall for about another hour, and in this particular experiment fell to about the same low level as in the control, but then it rose steeply, reached 42.4° C within 5 hr, and was still about 40° C another 10 hr later.

Thus two factors of a different nature are responsible for the rise in temperature which occurs when a Collison cannula is implanted into the lateral ventricle during pentobarbitone sodium anaesthesia with the head fixed to the stereotaxic instrument: sensory stimuli, associated with fixing the head and with the surgical procedures, and the actual introduction of the cannula into the ventricle. The sensory stimuli initiate the rise in temperature, but its continuation to the high level which is maintained for several hours is the result of cannulating the ventricle.

Once a cannula had been chronically implanted into the lateral ventricle, intraperitoneal pentobarbitone sodium anaesthesia caused the same fall and recovery of temperature as before implantation. In all subsequent experiments the intraventricular injections of drugs were therefore made on cats with chronically implanted Collison cannulas.

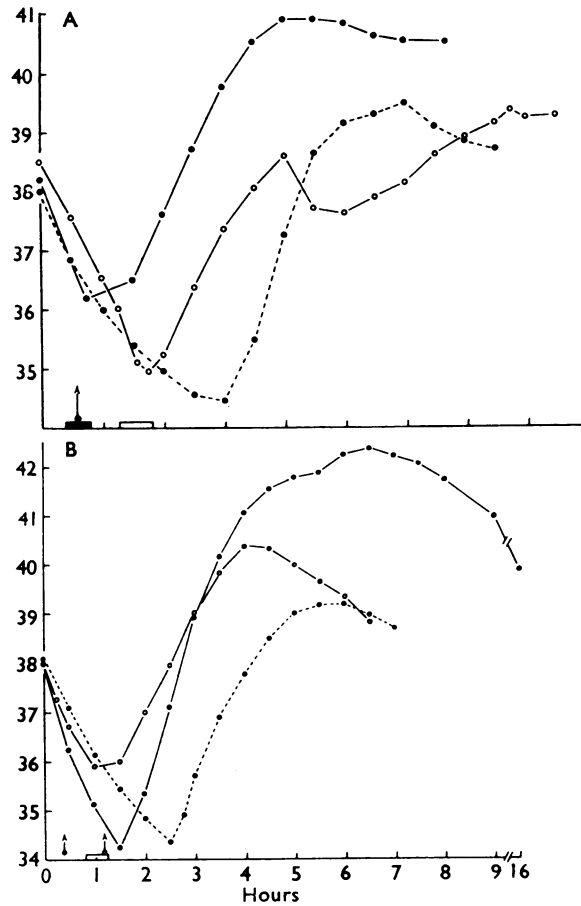

Fig. 1. Records of rectal temperature obtained from two anaesthetized cats. Each record begins approximately 15 min after an intraperitoneal injection of pentobarbitone sodium (33 mg/kg). Cat A: ●----●, Pentobarbitone sodium alone; ●——●, 4 days later. Cannulation of left lateral ventricle; solid horizontal bar indicates time (25 min) head was kept fixed to stereotaxic instrument and arrow (↕) moment of cannulation. ○——○, Another 11 days later; fixing head to stereotaxic instrument; open horizontal bar indicates time (30 min) head was kept fixed. Cat B: ● --- ●, Pentobarbitone sodium alone; ○——○, 4 days later. Sham cannulation. Open horizontal bar indicates time (20 min) head was kept fixed to stereotaxic instrument and arrow (↑) moment of implantation of sham cannula. ●——●, Another 11 days later. Removal of sham cannula and replacement by Collison cannula without fixing head to stereotaxic instrument. Arrow (↑) indicates moment of cannulation of ventricle.

Morphine

Intraventricular injections. When injected intraventricularly during the falling phase of temperature caused by pentobarbitone sodium anaesthesia, morphine caused a rise in rectal temperature with shivering and constriction of the ear vessels. The effect was obtained with 0.2–1 mg and sometimes with 0.1 mg. Shivering began in the flanks, sometimes within less than a minute, and within another few minutes spread over the

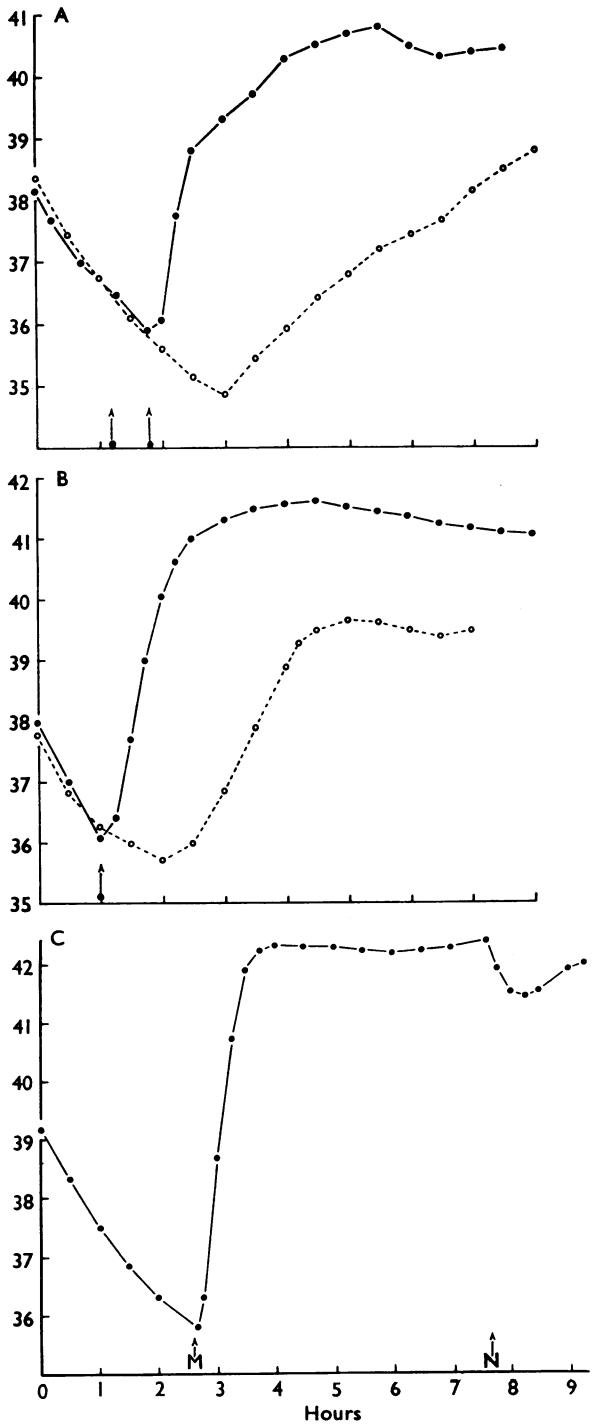

Fig. 2. Records of rectal temperature from three cats, A, B and C. Each record begins approximately 15 min after intraperitoneal injection of pentobarbitone sodium (33 mg/kg). ○---- ○, Pentobarbitone sodium alone; ●—— ●, intraventricular injections of morphine at the arrows; cat A, 0.1 mg at first and 0.2 mg at second arrow; cat B, 0.5 mg; cat C, 1 mg at the arrow (M), intraventricular injection of 1 mg nalorphine at the arrow (N).

whole body and became vigorous. Rectal temperature rose steeply during the first hour, sometimes as much as 6° C, finally reached 40°—more than 42° C and was maintained at this high level for several hours.

Figure 2A shows the effect of 0.1 and 0.2 mg morphine. With 0.1 mg the fall in temperature produced by the anaesthetic was not arrested; the cat did not shiver but there was some vasoconstriction in the ears which became less warm but not cold. With the subsequent injection of 0.2 mg, rectal temperature rose from 35.8° to 39.3° C during the first hour and finally to 40.8° C. Figure 2B, obtained on another cat, shows the steep rise in rectal temperature from 36.1° to 40.1° C in 1 hr, and finally to 41.6° C with 0.5 mg morphine. Figure 2C, from yet another cat, shows a rise from 35.8° to 42° C during the first hour and finally to 42.4° C following an intraventricular injection of 1 mg morphine. The interrupted curves in cats A and B were obtained a few weeks earlier than the continuous ones and show the effect of the anaesthesia alone.

With still higher doses (2–3 mg), shivering was not the only motor effect observed. A few minutes after shivering had spread over the whole body, scratching movements of the hind legs occurred which later became associated with wiping movements of the forelegs. Sometimes these movements occurred after an injection of only 1 mg.

Mehes (1939) and Königstein (1939) first described these movements following intracisternal or intraventricular injections of morphine in cats, and attributed them to an action on structures situated near the dorso-lateral surface of the upper cervical cord. It thus follows that when 2 or 3 mg, and sometimes when 1 mg, are injected intraventricularly, sufficient morphine passes through the foramina of Luschka into the subarachnoid space to excite these structures.

Perfusion through the third ventricle. Perfusion of morphine either from a lateral or from the third ventricle to aqueduct produced vigorous shivering and a rise in rectal temperature. Figure 3 shows the results of three experiments, two with morphine 1/1,000 perfused from lateral ventricle to aqueduct (A and B) and one with morphine 1/10,000 perfused from third ventricle to aqueduct (C).

When temperature had reached its maximal level on continued perfusion with morphine (1/1,000) temperature remained high or decreased slightly and shivering lessened or stopped. When perfusion was then switched over to that of artificial cerebrospinal fluid, shivering again increased or began and temperature rose. Such a rise is shown in experiment B of Fig. 3.

In none of these experiments with the aqueduct cannulated and the subarachnoid space excluded from the perfusion, did morphine produce the scratching and wiping movements seen on its intraventricular injection. They occurred, however, when the aqueductal cannula was removed and perfusion with morphine (1/1,000) was continued.

Nalorphine

Nalorphine (1 mg) had no effect on temperature when injected intraventricularly during pentobarbitone sodium anaesthesia, but it antagonized the hyperthermic effect produced by morphine similarly applied. Injected before the morphine it prevented the rise, injected after the morphine it was less effective.

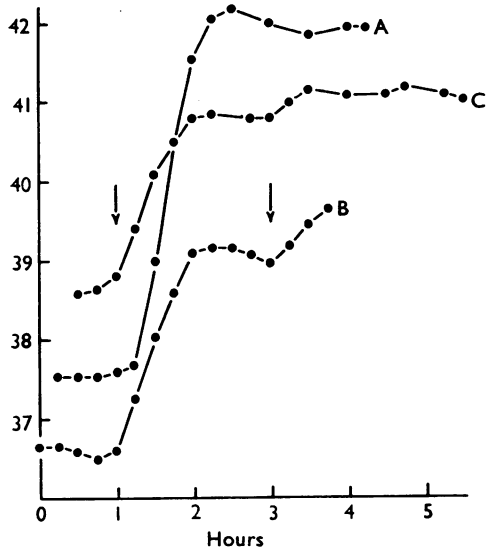

Fig. 3. Records of rectal temperature obtained from three cats anaesthetized with intraperitoneal injections of pentobarbitone sodium (33 mg/kg) during perfusion from left lateral ventricle (cat A and B) or from third ventricle (cat C) to aqueduct with artificial cerebrospinal fluid until the first arrow, and from then on with morphine (cat A and B, 1/1,000; cat C, 1/10,000). In cat B at the second arrow, return to perfusion with artificial cerebrospinal fluid. Rate of perfusion 0.05 ml./min.

An experiment with nalorphine injected before the morphine is illustrated in Fig. 4. The three temperature curves are from the same cat. The interrupted curve shows the effect of pentobarbitone sodium anaesthesia alone; the continuous curve with the solid circles shows the steep rise to 41.5° C in response to 1 mg morphine given intraventricularly while temperature was falling; and finally, the curve with the open circles shows

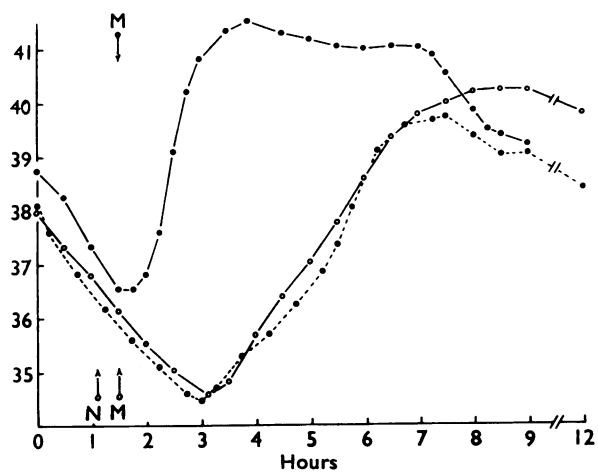

Fig. 4. Records of rectal temperature obtained from the same cat. Record (○——○) obtained 53, and record (●----●) 60 days after record (●——●). Each record begins approximately 15 min after intraperitoneal injection of pentobarbitone sodium (33 mg/kg). ●----●, Pentobarbitone sodium alone; ●——●, intraventricular injection of 1 mg morphine at arrow (M); ○——○, intraventricular injections of nalorphine 1 mg at arrow (N) and of morphine 1 mg at arrow (M).

the prevention of this rise by 1 mg nalorphine injected 25 min before the morphine. With longer intervals between the injections (90 min or more) the rise in temperature was reduced but no longer prevented. The effect of nalorphine thus passed off earlier than that of morphine.

Two experiments with nalorphine given 30 min after the morphine are illustrated in Fig. 5. In one, the nalorphine was given while temperature was rising at a rate of about 1° C in 10 min. Shivering became greatly reduced, and the rise in temperature was almost arrested for about 10 min; temperature then rose about 0.7° C in 20 min and another 0.3° C during the following 70 min. The subsequent steeper rise may indicate that the effect of nalorphine was wearing off. In the other experiment, temperature had risen to almost 42° C when the nalorphine was given. Shivering was stopped and temperature fell nearly 1° C during the following hour.

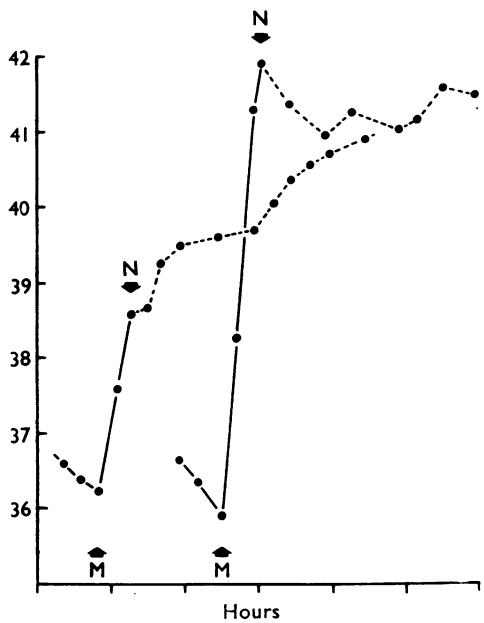

Fig. 5. Records of rectal temperature from two cats anaesthetized with intraperitoneal pentobarbitone sodium (33 mg/kg). The arrows indicate intraventricular injections of morphine 1 mg (M) and of nalorphine 1 mg (N). After nalorphine records continue as broken lines.

The effect of nalorphine given several hours after the morphine while temperature was maintained at over 42° C is illustrated in experiment Fig. 2C. Temperature fell about 1° C, but the effect wore off after an hour, again suggesting a relatively short-lasting action of nalorphine.

Ergotamine

Injected intraventricularly during pentobarbitone sodium anaesthesia at a time when the cat was not shivering, ergotamine (50 or 100 μg) produced shivering, usually after an interval of 5–17 min. When shivering was present it stopped for a few minutes but then became stronger than before the injection. In many experiments shivering became vigorous and spread over the whole body; temperature then rose several degrees, and the effect lasted for about an hour. In others shivering remained weak and confined to

the flanks; temperature then rose 0.2–0.3° C only, and the effect was over in less than 30 min. In a few experiments there was no shivering and no rise in temperature, and occasionally even a fall, or a fall preceded by a small rise. This happened during prolonged experiments when the ergotamine was given after temperature had recovered and was higher than 39° C. In these experiments it was always possible to provoke pronounced shivering and a rise in temperature with ergotamine when the intraventricular injection was preceded, 30 to 90 min earlier, by an intravenous injection of 18–36 mg pentobarbitone sodium. A second injection of ergotamine given after the effect of the first had subsided produced either a weaker or, more often, no response.

Figure 6 illustrates temperature responses to intraventricular ergotamine (100 μg). In cat A the ergotamine was injected 1.5 hr after the onset of anaesthesia during the falling phase of temperature; it resulted in vigorous shivering, constriction of the ear vessels and a rise in temperature of more than 2° C. A second injection given 2 hr later was less effective. In cat B, the injection was made nearly 4.5 hr after the onset of anaesthesia while temperature was rising and the cat was shivering. Shivering stopped for a few minutes but when it reappeared it became more vigorous than before and resulted in a steeper rise of temperature. A second injection given about 2 hr later was ineffective. In cat C, the ergotamine was injected about 6 hr after the onset of anaesthesia but was preceded by an intravenous injection of pentobarbitone sodium (18 mg) which had caused cessation of shivering and a fall in temperature. The ergotamine injection resulted in vigorous shivering with a rise in temperature. A second injection given 1 hr later was ineffective.

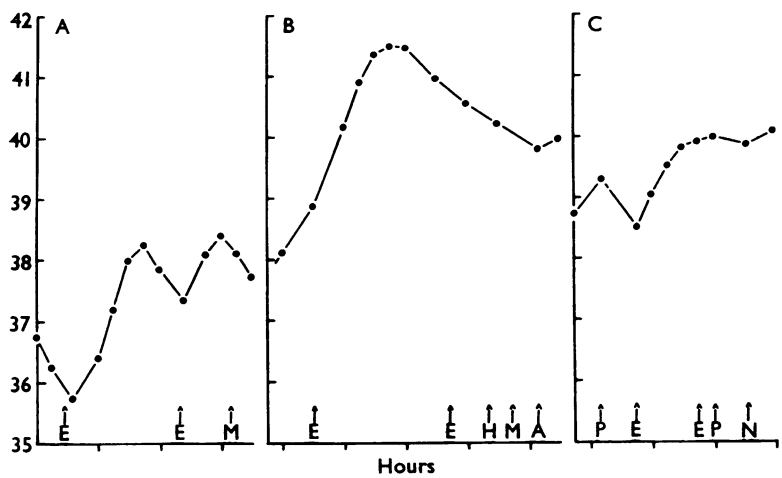

Fig. 6. Records of rectal temperature from three cats. Record of cat A begins about 1 hr, cat B about 3.5 hr and cat C about 5 hr after intraperitoneal injection of pentobarbitone sodium (33 mg/kg). Arrows indicate intraventricular injections of ergotamine 100 μg (E); of morphine 1 mg (M); of 5-HT 200 μg (H); of adrenaline 100 μg (A); of noradrenaline 100 μg (N); and intravenous injections of pentobarbitone sodium 18 mg (P).

The effect of ergotamine in unanaesthetized cats was similar and again varied greatly, as illustrated in Fig. 7. In cat B, the ergotamine produced, after an interval of 10 min, vigorous shivering and a rise in temperature of 1.3° C, whereas in cat C (upper curve) it produced no shivering and no rise in temperature.

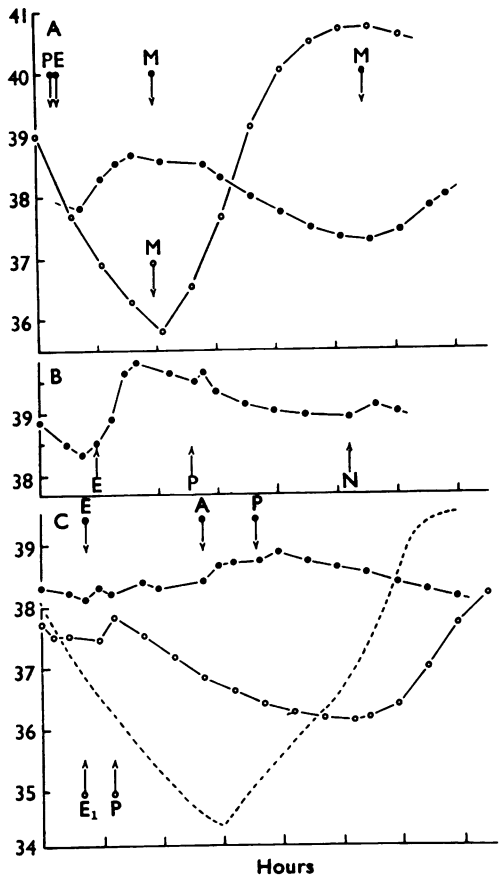

Fig. 7. Records of rectal temperature from three cats, A, B and C. Cat A, record (○——○) obtained 24 hr after record (● ●). Cat C, record (●——●) obtained 3, and record (○——○) 5 weeks after record (– – – –). Record (○——○) cat A and record (– – – –) cat C, begin approximately 15 min after intraperitoneal injection of pentobarbitone sodium (33 mg/kg). All others begin before anaesthetizing the cat. Arrows indicate intraventricular injections of ergotamine 100 μg (E); of ergotamine 20 μg (E_1); of adrenaline 100 μg (A); of noradrenaline 100 μg (N); and intraventricular injections of pentobarbitone sodium 33 mg/kg (P).

Effect of ergotamine on temperature responses produced by drugs

Monoamines. The results were similar in unanaesthetized cats and in cats anaesthetized with pentobarbitone sodium. Intraventricular adrenaline or noradrenaline (50 or 100 μg) which usually produces a fall in rectal temperature, no longer had this effect when given after an intraventricular injection of ergotamine (100 μg). Instead the catecholamines produced some shivering which began almost immediately after the injection, occurred usually in the form of bursts and continued often for not more than 10 min, but sometimes up to 30 min. During this time, temperature rose 0.1° to 0.3° C as illustrated in Figs. 6 and 7 at (A) and (N). This short-lasting " reversal " was weak and obtained only with the first injection of adrenaline or noradrenaline; subsequent injections of either catecholamine produced neither a rise nor a fall in temperature. In two out of eleven experiments this happened with the first injection and no " reversal " was observed.

On the other hand, a reversal was obtained when ergotamine itself had produced neither shivering nor a rise in rectal temperature. In the experiment illustrated in Fig. 8, ergotamine (50 μg) given intraventricularly during anaesthesia while temperature was falling, did not affect the slope of the fall, but adrenaline (50 μg) given intraventricularly 0.5 hr later caused shivering and a rise in temperature of 0.3° C. In the experiment of cat C in Fig. 7 (upper curve), a smaller " reversal " associated with shivering was obtained with adrenaline (100 μg) on an unanaesthetized cat in which ergotamine again had produced no response.

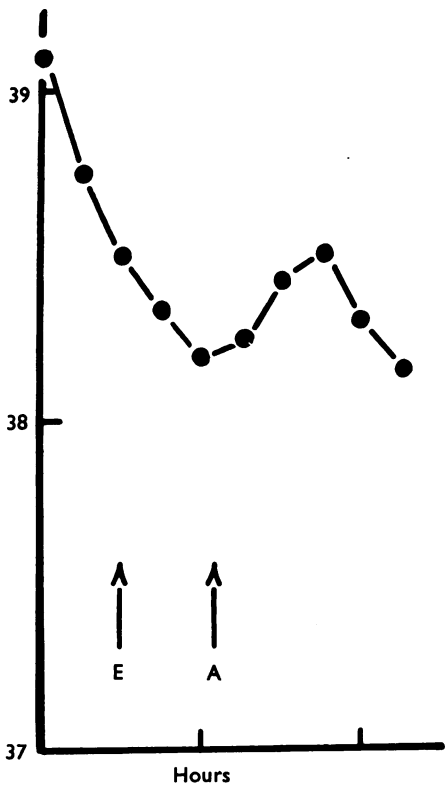

Fig. 8. Record of rectal temperature from a cat anaesthetized with intraperitoneal pentobarbitone sodium (33 mg/kg). Arrows indicate intraventricular injection of ergotamine 50 μg (E) and of adrenaline 50 μg (A).

The hyperthermic response usually obtained with an intraventricular injection of 5-HT (200 μg) was abolished, but not reversed by ergotamine, as illustrated in the experiment on cat B, Fig. 6.

Morphine. The strong hyperthermic response to an intraventricular injection of morphine 0.5 or 1 mg was abolished by ergotamine. This is shown on cats A and B in Fig. 6, and on cat A in Fig. 7, which gives in addition an indication of the duration of the ergotamine effect since the same dose of morphine (1 mg) was injected at three different intervals after the ergotamine. The curve with the solid circles shows the response of morphine when injected 1.5 and 5 hr after the ergotamine. No rise in temperature occurred at the 1.5 hr interval and a very sluggish rise, indicating that

sensitivity to morphine had just begun to return, at the 5.5 hr interval. After 24 hr the sensitivity to morphine had fully returned as shown by the curve with the open circles.

Pentobarbitone sodium. An intraventricular injection of ergotamine (100 μg) abolished but never reversed the fall in temperature produced by pentobarbitone sodium. For instance, when a small dose (18 mg) of pentobarbitone sodium was injected intravenously during a prolonged experiment in order to reinforce anaesthesia, temperature usually fell half a degree or more, but this did not happen after ergotamine as shown in the experiment on cat C in Fig. 6.

The effect was also shown when ergotamine was given a few minutes after the intraperitoneal injection of an anaesthetizing dose of pentobarbitone sodium, before temperature had time to fall. Ergotamine then prevented the long-lasting fall that would otherwise have occurred. Nevertheless the cat became fully anaesthetized. The temperature curve of such an experiment is shown on cat A in Fig. 7. In this experiment the ergotamine had caused vigorous shivering and a rise in temperature. It might therefore seem that its hyperthermic effect had simply overcome the hypothermic effect of the anaesthetic. This interpretation is not applicable to the results obtained when the ergotamine was injected into an unanaesthetized cat some time before pentobarbitone sodium anaesthesia was initiated. Two such experiments are illustrated on cats B and C in Fig. 7. In cat B, the pentobarbitone sodium was injected 1.5 hr after the intraventricular injection of ergotamine (100 μg) at a time when the vigorous shivering and the rise in temperature produced by the ergotamine was subsiding. Temperature remained high ; it continued to fall slightly at about the same rate as before the injection. The small rise immediately after the injection was caused by movements brought on by removing the cat from the cage in order to make the intraperitoneal injection. In cat C, the injection of ergotamine had produced no rise in temperature. Nevertheless, temperature did not fall, or at least not more than 0.6° C in more than 3 hr, following the intraperitoneal injection of an anaesthetizing dose of pentobarbitone sodium. In both experiments the cats again became deeply anaesthetized for many hours.

Ergotamine was effective in doses smaller than 100 μg. In the experiment of cat C, 20 μg was given intraventricularly 0.5 hr before the cat was anaesthetized (curve with open circles). Temperature fell more gradually, and not as deeply as after the injection of pentobarbitone sodium alone.

DISCUSSION

The mechanism by which fixing the head to the stereotaxic instrument or implanting a cannula into a lateral ventricle produces a rise in body temperature has not been investigated. The stimulus responsible for the rise is unlikely to be the same in both instances. Fixing the head to the ear bars and mouthpiece of a stereotaxic instrument gives rise to strong sensory stimuli. They in turn may affect the activity of monoaminergic neurones which end in the anterior hypothalamus, either by inhibition of fibres that release catecholamines or by excitation of those that release 5-HT, or by both mechanisms. Implantation of the cannula may act through the brain injury produced when

the cannula passes the cerebral hemisphere. The injury need not necessarily act as a neuronal stimulus but hyperthermic substances produced in the injured tissue or derived from clotting of the blood may pass into the cerebral ventricles. Or the implantation may be associated with sudden pressure changes in the ventricle. This mechanical stimulus may act on nerve endings in the ventricular lumen. These nerve endings have been known to exist for more than 50 years and have recently been re-examined in electromicroscopic studies by Leonhardt & Lindner (1967), who reviewed the older light microscopic findings. Sudden pressure changes in the ventricles may well act on these endings and thereby activate monoaminergic fibres which end in the hypothalamus. This would not be the only instance in which a brief mechanical stimulus produces a persistent effect on body temperature. Another example, with an effect on body temperature in the opposite direction, is that of applying brief light pressure to the region of the fourth ventricle near the aqueduct, or merely touching this region. This was found to result in cessation of shivering with a fall in temperature sometimes lasting for several hours. It was explained by mechanical stimulation of monoaminergic nerve fibres which release noradrenaline and end in the anterior hypothalamus (El Hawary, Feldberg & Lotti, 1967).

In cats, morphine seems to give the same temperature response whether injected into the cerebral ventricles or systemically; hyperthermia produced by subcutaneous injections was described more than 30 years ago by Helferich (1935). The hyperthermia produced by morphine injected into the cerebral ventricles is readily attributable to an action on the hypothalamus because it occurred when morphine was perfused through the third ventricle. It probably also acts through the hypothalamus when injected subcutaneously.

The pertinent problem is: how does the morphine act? Does it affect those nerve cells in the anterior hypothalamus, excitation of which sets up the train of events that leads to a rise in temperature, or—since morphine reduces the monoamines in the hypothalamus—does it act indirectly through the release of 5-HT from the monoaminergic nerve fibres which end on these cells?

With the evidence so far available it is not possible to decide between these alternatives. The finding that morphine affects temperature in the same way as 5-HT when acting on the hypothalamus of cats and rats—raising it in cats and lowering it in rats—is in accord with the view that it acts indirectly through release of this monoamine, but it could also be explained by a direct 5-HT like action on the hypothalamus. Similarly, the finding that, in cats, the hypothalamus, after intraventricular ergotamine, becomes insensitive not only to the hyperthermic action of 5-HT but also to that of morphine can be explained either way. And so can the difference in potency of nalorphine according to whether it is given before or after the morphine. Given first, nalorphine was found to prevent the action of morphine, given after the morphine it was less effective. If nalorphine were to prevent the release of 5-HT it should be less effective when given after the morphine, because 5-HT has then been released and would continue to act for some time. On the other hand, if morphine were to act directly, nalorphine, which has a much shorter-lasting action should also be less effective when morphine had had time to penetrate the brain first.

Further evidence in favour of either a direct or an indirect action may be obtained by examining the temperature effects of morphine injected intraventricularly in species other than cats and rats. In dogs and monkeys in which intraventricular 5-HT raises temperature, morphine given systemically lowers temperature (Schaumann, 1957). If it were to have this action also on intraventricular injection it could not be caused by release of 5-HT from the hypothalamus, at least not in these species.

The problem of attributing the temperature effects of morphine to release of the monoamines in the hypothalamus is further complicated by the fact that morphine releases not only 5-HT but the catecholamines as well, which in cats have a hypothermic effect. The problem will probably be solved only by demonstrating either the release, or the absence of the release, of the monoamines on perfusion of morphine through the third ventricle.

Ergotamine, considered to be the classical α-receptor blocking agent in peripheral tissues exerts a blocking effect also on the hypothalamus. However, it reversed and then abolished the hypothermic effect not only of adrenaline but of noradrenaline as well. Therefore the widely accepted concept of α and β-receptors developed for the peripheral actions of the catecholamines may not extend to the hypothalamus and possibly also not to other central sites on which the catecholamines act. It may not be justified, however, from the results so far obtained to draw conclusions about the presence or absence of these receptors in the hypothalamus because the blocking effect of ergotamine in the hypothalamus appears not to be specific for the catecholamines.

The finding that intraventricular ergotamine prevented the fall in temperature produced by an anaesthetizing dose of pentobarbitone sodium, but not the anaesthesia itself, is in accord with the view that the hypothermia of anaesthesia is brought about in the main by release of the monoamines in the hypothalamus. The anaesthetics probably release all three, noradrenaline, adrenaline and 5-HT, but the action of the released catecholamines predominates, at least in cats and dogs: therefore the fall in temperature. Three recent observations have been explained on these lines. In the rabbit and sheep, which lack an efficient hypothermic monoamine, pentobarbitone sodium produces anaesthesia without a significant fall in temperature (Ruckebush, Grivel & Laplace, 1965 ; Feldberg & Lotti, 1967a), whereas in the rat, in which all three monoamines exert a hypothermic effect when acting on the hypothalamus, it produces a deep fall (Feldberg & Lotti, 1967b). The third observation concerns the action of tranylcypromine. In cats and dogs this inhibitor of monoamine oxidase prevents the hypothermia of anaesthesia (Feldberg, Hellon & Lotti, 1967 ; Feldberg & Lotti, 1967a). In both species the 5-HT but not noradrenaline seems to be a substrate for brain monoamine oxidase (Vogt, 1959 ; Spector, Shore & Brodie, 1960 ; Pscheidt, Morpurgo & Himwich, 1964). Therefore the 5-HT released by anaesthetics is no longer destroyed. As it accumulates in the hypothalamus it is able to overcome the hypothermic effect of the catecholamines, which are released as well but which are not prevented from being destroyed. The experiments with ergotamine have now brought to light another condition in which the hypothermia may be prevented during anaesthesia, but the underlying mechanism is a different one: the hypothalamus is rendered insensitive to the action of the released monoamines.

The fall in temperature produced by pentobarbitone sodium was not converted into a rise whereas the hypothermic effects of intraventricular noradrenaline and adrenaline

were initially reversed, although the reversal was weak and short-lasting. This discrepancy is at present not explained, and it is necessary to keep in mind the apparently unspecific blocking action of ergotamine on the hypothalamus. If the hypothermia produced by pentobarbitone sodium resulted from a direct action of the anaesthetic on the hypothalamus it would probably also be prevented by ergotamine. So the results obtained with this adrenergic blocking agent, although in accord with the theory that the fall of temperature in anaesthesia results from release of the hypothalamic monoamines, could be explained differently.

SUMMARY

1. Morphine, nalorphine and ergotamine were injected into the cerebral ventricles of cats while rectal temperature was recorded.

2. In cats anaesthetized with pentobarbitone sodium the stimulus of fixing the head to the ear bars and mouthpiece of a stereotaxic instrument and of implanting a cannula into a lateral ventricle produced shivering and a rise in temperature. Intraventricular injections were therefore administered to cats with a chronically implanted Collison cannula.

3. Morphine (0.2–1 mg) injected intraventricularly into cats anaesthetized with pentobarbitone sodium produced vigorous shivering and a steep long-lasting rise in rectal temperature. The pyrogenic effect was also obtained when morphine was perfused through the third ventricle.

4. In larger doses, intraventricular injections of morphine (2–3 mg) produced in addition scratching and wiping movements of the legs. As they are known to result from an action on structures near the dorso-lateral surface of the cervical cord, sufficient morphine must have entered the subarachnoid space to produce these movements.

5. Nalorphine (1 mg) injected intraventricularly prevented the shivering and hyperthermia produced by morphine similarly applied. The nalorphine-morphine antagonism was less pronounced when morphine was injected first and had exerted its pyrogenic effect.

6. Ergotamine (100 μg) injected intraventricularly into anaesthetized or unanaesthetized cats produced shivering and a rise in temperature. In addition, the hypothermic responses to intraventricular adrenaline and noradrenaline were first reversed and then abolished; the hyperthermic responses to intraventricular 5-HT and morphine were abolished as well.

7. An intraventricular injection of ergotamine (100 μg) into an unanaesthetized cat prevented the hypothermia usually produced by the intraperitoneal injection of an anaesthetizing dose of pentobarbitone sodium; yet the cat became fully anaesthetized.

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