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TEMPERATURE CHANGES PRODUCED BY AMINES INJECTED INTO THE CEREBRAL VENTRICLES DURING ANAESTHESIA

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Recently we found that the three amines, 5-hydroxytryptamine (5-HT), adrenaline and noradrenaline, which occur naturally in the hypothalamus, affect body temperature when injected into the cerebral ventricles of an unanaesthetized cat: 5-HT raises and the catecholamines lower temperature. The hypothermic effect of the catecholamines was obtained in cats with normal temperature, as well as in those in which fever had been produced by bacterial pyrogens or 5-HT applied by the intraventricular route. The effects of the amines were attributed to their action on the hypothalamus, a conclusion supported by the finding that, when injected in much smaller amounts directly into the anterior hypothalamus, these amines caused similar changes in temperature (Feldberg & Myers, 1963, 1964). A hyperthermic effect of 5-HT when acting from the liquor spaces of the brain had been observed earlier by Canal & Ornesi (1961), who injected this amine intracisternally in unanaesthetized rabbits.

The present experiments were undertaken to find out if the hypothalamus retains its sensitivity to the amines and bacterial pyrogens under anaesthesia when temperature regulation is abolished and the animal has become poikilothermic. The two anaesthetics used were pentobarbitone sodium and chloralose, and the amines as well as the bacterial pyrogens were injected into the cannulated cerebral ventricles during surgical anaesthesia. This paper also incorporates experiments concerning the effect on temperature of the two anaesthetics themselves when given by the intraventricular route.

METHODS

In cats of both sexes, weighing 2·6–3·4 kg, a Collison cannula (Feldberg & Sherwood, 1954) was aseptically implanted under pentobarbitone sodium anaesthesia into the left lateral ventricle of the brain. After a recovery period of at least one week the cats were used for experiments at 5- to 15-day intervals. Housing and fasting of the cats, as well as the measurements and recording of rectal temperature, were the same as described previously

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(Feldberg & Myers, 1964). The experiments were carried out at room temperature, which ranged between 21 and 24° C.

In all experiments basal temperature was recorded for 1 hr before the cats were either anaesthetized or given intraventricular injections. Anaesthesia was induced by intraperitoneal pentobarbitone sodium or by intravenous chloralose. The chloralose solution was injected into the cephalic vein exposed by a small skin incision made under light ethyl chloride anaesthesia.

Substances injected into the cerebral ventricles. The two pyrogens used, typhoid AB vaccine (Burroughs Wellcome) and *Shigella dysenteriae* (Humphrey & Bangham, 1959), were from the same samples as used in the previous experiments. The adrenaline and noradrenaline were the bitartrate, and the 5-HT was the creatinine sulphate. The values for these amines given in the text refer to the salts. The pyrogens, the amines and the chloralose were injected in a volume of 0·1 ml. followed by an injection of 0·05 ml. 0·9 % NaCl solution. Pentobarbitone sodium is soluble only in strong alkaline solution. However, 12 mg/ml. is brought into solution if the pH is adjusted to 8·5 and the pentobarbitone sodium was injected in a volume of 0·25 ml. of such a solution containing 3 mg. All substances were dissolved or diluted in pyrogen-free 0·9 % NaCl solution, and the syringes, needles, and all glassware used were rendered pyrogen-free by standard heating procedures.

RESULTS

Pentobarbitone sodium anaesthesia

An intraperitoneal injection of an anaesthetic dose of pentobarbitone sodium into a cat kept at room temperature and not warmed by external heat produces a profound fall in rectal temperature, but the hypothalamus retains its reactivity to pyrogens as well as to the three amines, 5-HT, adrenaline and noradrenaline, injected intraventricularly. This is illustrated in Fig. 1, which gives for each of two cats, *A* and *B*, three records of rectal temperature which were obtained at weekly intervals. For both cats control records (filled circles on interrupted lines) illustrate the effect on rectal temperature of an intraperitoneal injection of an anaesthetic dose of pentobarbitone sodium (33 mg/kg). A few minutes after the injection the temperature begins to fall and during the following 2–3 hr falls steadily to between 35 and 33° C, whilst respiration slows to between 16 and 12/min. Temperature is maintained at the low level for about 1 hr; it then begins to rise, reaching its normal level within 5–6 hr. Sometimes the temperature rises above the normal level. With the rise of temperature, shivering sets in, becomes quickly vigorous and continues in this way throughout the period of rising temperature. As the temperature approaches normal, the cats show signs of awakening.

After an interval of 1 week the same dose of pentobarbitone sodium is injected intraperitoneally in each cat (records open circles). In cat *A*, this injection is followed by an intraventricular injection of 0·1 ml. 1/1000 typhoid vaccine at a time when the temperature has fallen to 34·4° C. After a latency of 1 hr the temperature rises rapidly and normal temperature is attained within an hour. However, the rise continues for several

hours until a fever level of over 41° C is reached, which is then maintained for many hours. Throughout the rise and during the period of elevated temperature the cat shivers and its ear vessels are constricted. The strong hyperthermic effect of the pyrogen injection is brought out in the figure by comparison with the temperature record obtained a week earlier when no pyrogen had been injected during the anaesthesia.

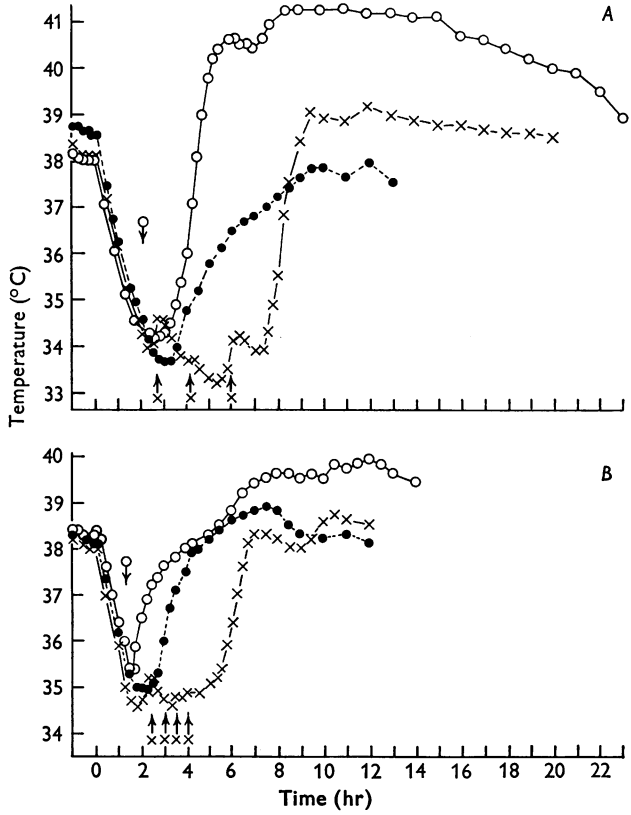

Fig. 1. Three records of rectal temperature obtained, at weekly intervals, on each of two cats *A* and *B*. At zero hour 33 mg/kg pentobarbitone sodium injected intraperitoneally in each experiment.
●----●, Pentobarbitone sodium alone; ○——○, at the arrow (♀) an intraventricular injection in cat *A* of 0·1 ml. 1/1000 typhoid vaccine and in cat *B* of 200 μg 5-HT; ×——×, at each arrow (♀) an intraventricular injection in cat *A* of 50 μg adrenaline and in cat *B* of 50 μg noradrenaline.

In cat *B*, the pentobarbitone sodium injection is followed by an intraventricular injection of 200 μg 5-HT, but this time during the phase of falling temperature before the lowest point had been reached. In contrast to the long latency after the typhoid-vaccine injection in cat *A*, there is a

latency of only a few minutes before the fall is reversed and a rapid rise ensues. Normal temperature is reached within 3½ hr but the rise continues to a level of nearly 40° C; this temperature is then maintained for several hours. Again comparison with the record obtained a week earlier when no 5-HT had been injected during the anaesthesia illustrates the pyrogenic effect of the 5-HT. During the rise the cat shivers and the ear vessels are constricted. Once the temperature has reached the high level, shivering, however, ceases. In this respect the effect of 5-HT differs from that of the typhoid vaccine because after its injection shivering continues throughout the period of elevated temperature.

After another interval of 1 week the same dose of pentobarbitone is again given to each cat (records crosses on full lines) and during the ensuing anaesthesia intraventricular injections of adrenaline are given to cat *A*, and of noradrenaline to cat *B*, with the result that the return to normal temperature is postponed. Three injections of 50 μg adrenaline are given to cat *A* at about 1½ hr intervals. The first injection is given when the temperature, after having fallen to the lowest point, 34° C, begins to rise and has reached 34·5° C. The injection reverses the rise and the temperature falls to 33·6° C. With the second injection there is a further fall to 33·2° C. When the temperature rises again, the third injection is given; it interrupts and delays this rise for over an hour. To cat *B*, four injections of 50 μg noradrenaline are given at about half-hourly intervals; they postpone the return to normal temperature for over 2 hr.

Intraperitoneal pentobarbitone sodium given during fever. Not only normal temperature, but also temperature elevated by intraventricular injections of either bacterial pyrogens or 5-HT is lowered by intraperitoneal pentobarbitone sodium. But the fall in temperature is followed after a relatively short period by a rise beyond the fever level recorded at the time of injection. Figure 2 illustrates this double effect on temperature of pentobarbitone sodium injected during fever produced by intraventricular typhoid vaccine (*A*), *Shigella* (*B*), and 5-HT (*C*). The experiment with *Shigella* illustrates in addition the sensitivity to intraventricular adrenaline given after the temperature had climbed to 41·5° C; an injection of 50 μg produces a fall of over 2° C.

Chloralose anaesthesia

Like pentobarbitone sodium, chloralose in anaesthetic doses produces a profound fall in rectal temperature and again the hypothalamus retains its reactivity to bacterial pyrogens, 5-HT, adrenaline and noradrenaline.

If the cat is kept at room temperature and not warmed by external heat, the fall in rectal temperature increases with increasing doses. This is illustrated in Fig. 3 for 45, 50 and 60 mg/kg. The effects of 45 and 50 mg/kg

are obtained on the same, that of 60 mg/kg on another cat. With 45 mg/kg the lowest temperature reached is 33·5° C, with 50 mg/kg 32·4° C, and with 60 mg/kg 30·8° C. The duration of hypothermia also increases with the dose injected. Following the injections of chloralose there is also a progressive slowing of respiration, as the temperature falls, and the rate

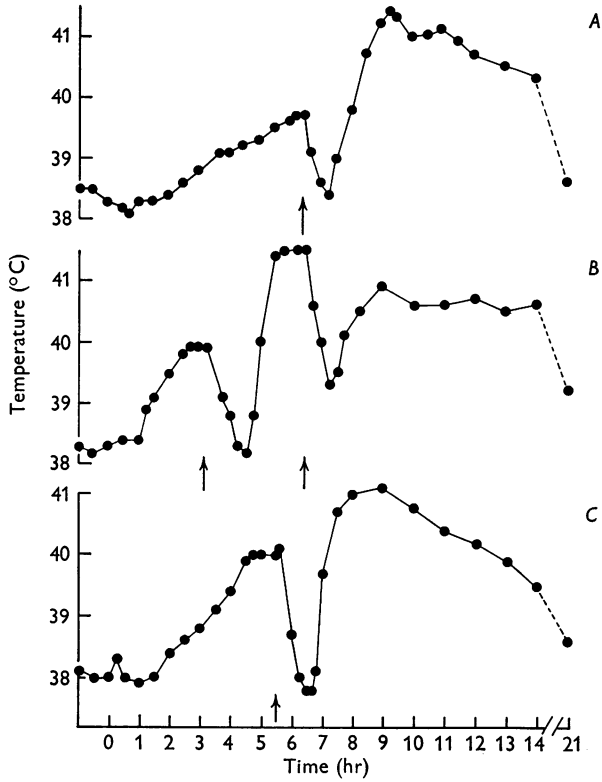

Fig. 2. Records of rectal temperature of three cats. At zero hour fever produced by intraventricular injections in cat *A* of 0·1 ml. 1/1000 typhoid vaccine, in cat *B* of 30 ng *Shigella d.* and in cat *C* of 200 μg 5-HT. At the arrows in *A* and *C*, and at the first arrow in *B*, intraperitoneal injection of 33 mg/kg pentobarbitone sodium. At the second arrow in *B*, intraventricular injection of 50 μg adrenaline.

declines to 6 or even 4/min. With the rise of temperature respiration again accelerates. After an intravenous injection of 70 mg/kg the temperature falls below 30° C and respiration becomes so slow, 2/min or less, that external heat has to be applied, for instance, by placing the cat on a heated table and under a heat lamp, in order to prevent death from respiratory failure.

During recovery from the chloralose anaesthesia vigorous myoclonic contractions develop which often involve the musculature of the whole

body. The contractions occur either continuously or intermittently. When they occur intermittently they are easily brought on by a sudden noise or by touching the animal. Shivering, seen regularly during recovery from pentobarbitone sodium anaesthesia with the rise in temperature, occurs occasionally and is not intense.

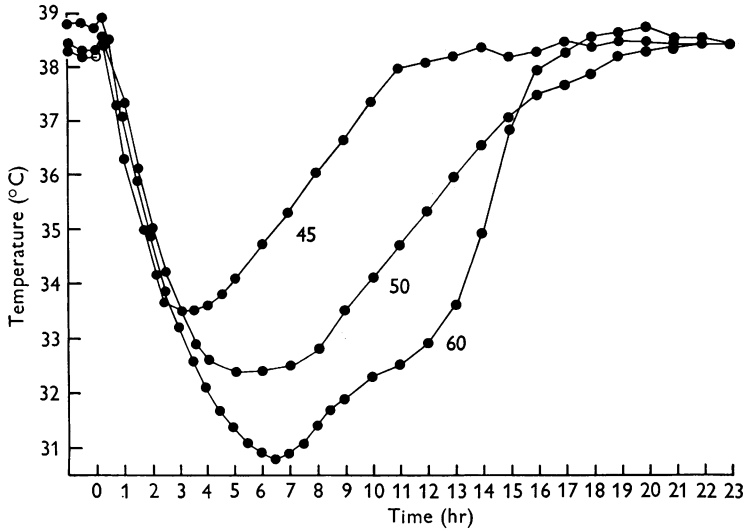

Fig. 3. Effect of intravenous injections at zero hour, of 45, 50 and 60 mg/kg chloralose on rectal temperature of cats. The records showing the effect of 45 and 50 mg/kg obtained from the same cat at an interval of one month. The records are used as controls for the experiments of Figs. 4, 5 and 6.

Intraventricular injections of bacterial pyrogens, typhoid vaccine or *Shigella*, counteract the hypothermic effect of chloralose. Temperature begins to rise after a latency of about 1 hr, and during the following hours climbs to fever level whilst respiration accelerates, ear vessels constrict and vigorous shivering occurs. The effect on rectal temperature of 0·1 ml. 1/1000 typhoid vaccine injected intraventricularly during chloralose anaesthesia is shown in Fig. 4, together with a control record obtained in the same cat by chloralose alone. A comparison of the two records brings out the strong pyrogenic action of typhoid vaccine in chloralose anaesthesia. When comparing the two records it should be noted that the control is obtained with a lower dose of chloralose, 50 mg/kg, rather than 70 mg/kg, because with the higher dose the fall in temperature is so great that, if not reversed by either external heat or pyrogens, the animal would die.

Intraventricular 5-HT also exerts its pyrogenic effect when the cat is anaesthetized with chloralose; the effect differs from that of the bacterial pyrogens similarly applied in that the latency is shorter. The rise begins

within about 10 min after the injection and, as in unanaesthetized cats, is biphasic. During the rise respiration accelerates, the ear vessels constrict and shivering occurs. Figure 5 illustrates the effect of intraventricular 5-HT on rectal temperature in two experiments carried out on the same cat. The one record shows the effect of a single injection of 200 μg, the

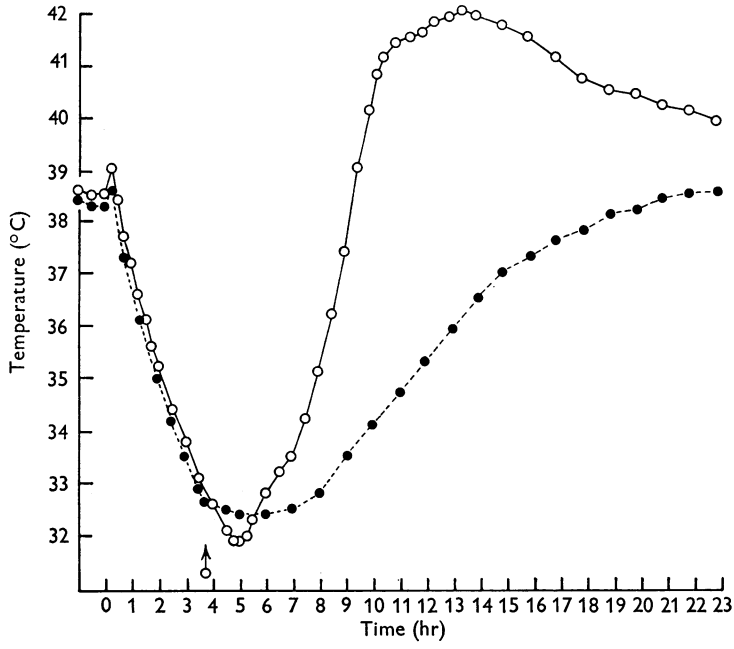

Fig. 4. Two records of rectal temperature obtained from the same cat at an interval of 6 weeks. At zero hour intravenous injection of chloralose in both instances. ●----●, 50 mg/kg chloralose alone; ○——○, 70 mg/kg chloralose followed at the arrow (⇧) by an intraventricular injection 0·1 ml. 1/1000 typhoid vaccine.

other of two such injections given 5 hr apart. For comparison a control record is included showing the effect of chloralose alone on the same cat, the dose again being smaller (60 mg/kg) than used in the two experiments with 5-HT (70 mg/kg).

Adrenaline or noradrenaline injected intraventricularly exert their hypothermic action also in chloralose anaesthesia. This is illustrated in Fig. 6, which for comparison includes a control record obtained in the same cat for the effect of chloralose alone. For the first 5 hr until the injection of 50 μg adrenaline the two curves run parallel. The injection given after the temperature has begun to rise results in a renewed fall and this happens again with the subsequent injection of 50 μg noradrenaline given 4 hr later. The two injections have postponed the return to normal temperature for

over 10 hr. Figure 6 also illustrates the transient hyperthermia regularly seen following the hypothermic effects of the catecholamines as shown by the fact that the temperature continues to rise for about 1° C above normal temperature.

By injecting alternately 5-HT and either noradrenaline or adrenaline it

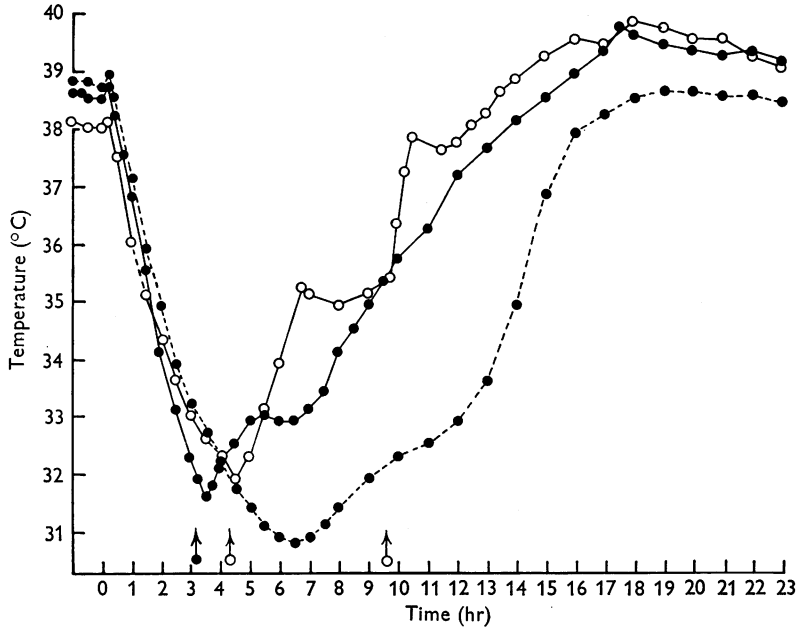

Fig. 5. Three records of rectal temperature obtained from the same cat at about weekly intervals. At zero hour intravenous injection of chloralose in all instances. ●----●, 60 mg/kg chloralose alone; ●——●, 70 mg/kg chloralose followed at the arrow (↑) by an intraventricular injection of 200 μg 5-HT; ○——○, 70 mg/kg chloralose followed at each arrow (↑) by an intraventricular injection of 200 μg 5-HT.

is possible to raise or lower and thus to control temperature during the hypothermia of chloralose anaesthesia. An example of this control is shown in the experiment illustrated in Fig. 7, where an injection of 5-HT is followed by that of noradrenaline, which in turn is followed by that of 5-HT.

If, after an intravenous injection of chloralose 70 mg/kg, temperature is allowed to fall below 30° C and respiration slows to 2/min or less, intraventricular injections of 200 μg 5-HT no longer raise temperature, or at most raise it only slightly.

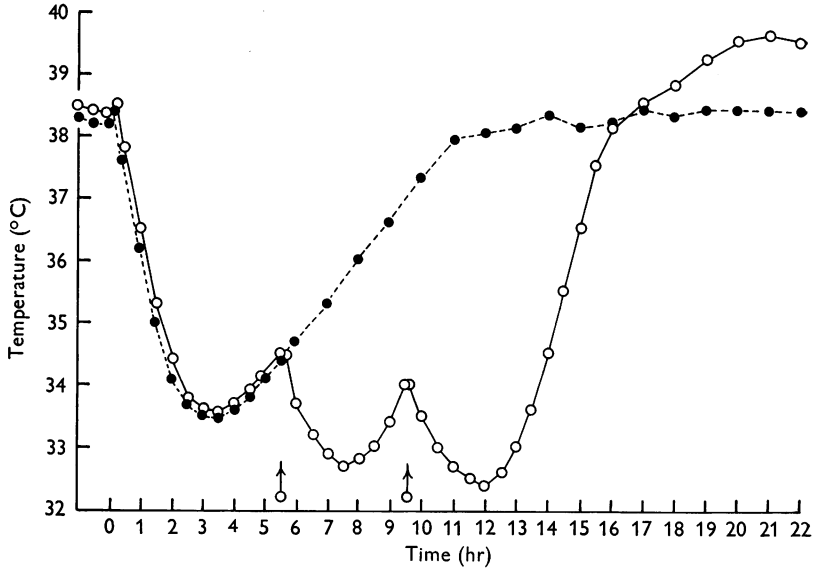

Fig. 6. Two records of rectal temperature obtained from the same cat at an interval of 1 week. At zero hour intravenous injection of chloralose 45 mg/kg in both instances. ●----●, Chloralose alone; ○——○, chloralose followed by an intraventricular injection of 50 μg adrenaline at the first, and of 50 μg noradrenaline at the second arrow.

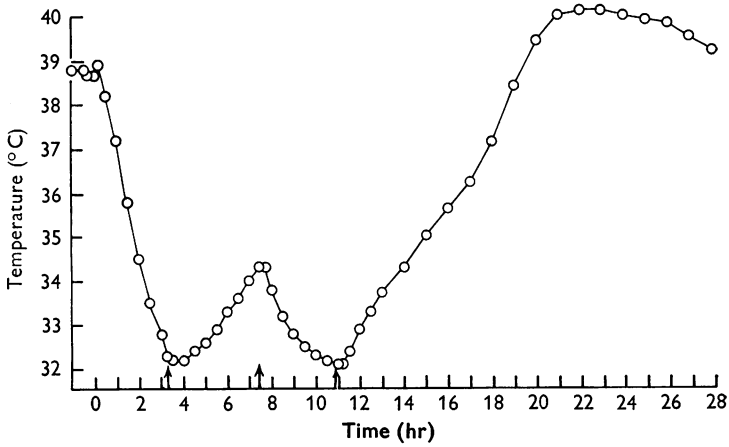

Fig. 7. Record of rectal temperature obtained from a cat given at zero hour an intravenous injection of chloralose 60 mg/kg followed by intraventricular injections of 200 μg 5-HT at the first, of 100 μg noradrenaline at the second, and of another 200 μg 5-HT at the third arrow.

Pentobarbitone sodium and chloralose injected into the cerebral ventricles

Changes in temperature similar to those produced with anaesthetic doses of intraperitoneal pentobarbitone sodium or of intravenous chloralose are obtained with very small amounts of these anaesthetics injected into the cerebral ventricles. Injected in this way pentobarbitone sodium produces a biphasic effect: a fall in temperature of relatively short duration followed by a rise beyond the pre-injection level. The effect resembles that seen in the experiments in which pentobarbitone sodium is injected intraperitoneally during fever (see page 467). Intraventricular chloralose produces only a fall of temperature. After the intraventricular injection of pentobarbitone sodium or chloralose, the cat lies down and often curls up. Most of the time the eyes are closed and the cat appears to be asleep but is easily roused. This soporific effect of intraventricular injections of small amounts of anaesthetics has been described previously (Feldberg, 1957, 1959).

Figure 8*A* illustrates the effects on rectal temperature of four successive injections of 3 mg pentobarbitone sodium. Each injection lowers the

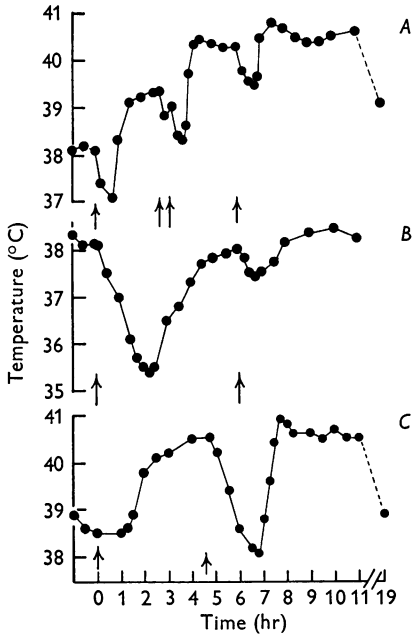

Fig. 8. Three records of rectal temperature obtained from three cats. Cat *A*: at each of the four arrows an intraventricular injection of 3 mg pentobarbitone sodium. Cat *B*: an intraventricular injection at the first arrow of 0·8 mg chloralose and at the second arrow of 100 μg noradrenaline. Cat *C*: an intraventricular injection at the first arrow of 30 ng *Shigella d.* and at the second arrow of 0·9 mg chloralose.

temperature but the fall is followed by a rise beyond the pre-injection level if the interval between the injections is kept sufficiently long, as between the first and second, and between the third and fourth injection. After the first injection the temperature falls from 38·2 to 37·1° C and then rises to 39·3° C, after the second and third injection it falls to 38·3° C and then rises to 40·2° C, and finally after the fourth injection it falls to 39·4° C and rises to 40·7° C. With each rise vigorous shivering sets in and the ear vessels constrict, whereas with each fall shivering stops and the ear vessels dilate.

Figure 8*B* shows the long-lasting fall in temperature produced by an intraventricular injection of 0·8 mg chloralose. The temperature falls about 2·5° C, and the return to normal takes over 5 hr, but the temperature does not rise beyond the pre-injection level. During the rising phase of temperature, there is some shivering and the ear vessels which had dilated during the falling phase constrict. The figure illustrates that the hypothermic effect of 0·8 mg chloralose is more pronounced and longer lasting than that of 100 μg noradrenaline similarly applied.

Figure 8*C* illustrates the effect of intraventricular chloralose (0·9 mg) given during fever produced by *Shigella* similarly applied. Again the temperature falls about 2·5° C within 2 hr, but the subsequent rise is much steeper than in the corresponding experiment on the non-feverish cat of Fig. 8*B*. The rise is associated with intense shivering which continues after the temperature has reached its highest level.

DISCUSSION

Previously we have shown that, injected into the cerebral ventricles of unanaesthetized cats, 5-HT raises and the catecholamines, adrenaline and noradrenaline, lower body temperature. The effects were attributed to an action on the hypothalamus and the theory was put forward that the three amines play a role in the hypothalamic control of body temperature, and further that any changes in temperature brought about by the hypothalamus would have to be considered in the light of this new concept of chemical regulation in this part of the brain.

Anaesthesia results in a fall in temperature and, as shown with chloralose, the extent of the fall depends on the amount of anaesthetic injected. How can the new concept of temperature regulation be applied to this special instance? First, the fall in temperature can be attributed to an action of the anaesthetics on the hypothalamus because both chloralose and pentobarbitone sodium lower body temperature when injected into the cerebral ventricles in doses far too small to be effective on systemic application. In the present experiments such a hypothermic effect was obtained with less than 1 mg chloralose, or with 3 mg pentobarbitone sodium

The fall in temperature, however, cannot be explained on the assumption that in 'anaesthetizing the hypothalamus' the anaesthetics render this structure insensitive to the amines, because the present experiments show that the hypothalamus retains its sensitivity to the amines under both chloralose and pentobarbitone sodium anaesthesia. To explain the fall in temperature in the light of the new concept one would have to assume that the anaesthetics act by modifying the release of the amines in the hypothalamus or at least act mainly in this way. This would also provide a plausible explanation of why there are some differences between the changes in temperature under chloralose and pentobarbitone sodium anaesthesia.

With chloralose the sole effect on temperature is a fall, which could be explained by either a release of the catecholamines or an inhibition of the release of 5-HT, or both. With pentobarbitone sodium the fall is followed in certain circumstances by a rise beyond the pre-injection level, and this rise is associated with vigorous shivering. This happens each time small amounts of pentobarbitone sodium are injected into the cerebral ventricles so that the temperature finally reaches fever level. This also happens when pentobarbitone sodium is injected intraperitoneally in anaesthetic doses during fever produced by bacterial pyrogens. The fall in temperature is then followed, after a relatively short time, by a rise beyond the level of fever existing before anaesthesia was induced. Thus pentobarbitone sodium clearly has a double effect on temperature which would require a release or increased release of the catecholamines as well as of 5-HT. A release of 5-HT would appear to occur also in afebrile cats when anaesthesia is produced by intraperitoneal pentobarbitone sodium because in these cats shivering occurs regularly, not during the initial fall in temperature, but later when the temperature begins to rise again. This shivering may well be the result of the release of 5-HT since this amine is known to produce shivering when applied by the intraventricular route. The phenomenon of pentobarbitone sodium shivering has been known for a long time, has been used for studying the mechanism of shivering, and has been shown to be abolished by small amounts of catecholamines given intraventricularly (Domer & Feldberg, 1960). On the other hand, in chloralose anaesthesia, shivering is not usually associated with the return to normal temperature and, if it occurs, is rarely vigorous.

Whether an anaesthetic produces a fall in temperature or a fall followed by a rise associated with shivering the fundamental mechanism could well be the same and could consist of a release of the amines within the hypothalamus. In fact, with both chloralose and pentobarbitone sodium, there may be from the beginning a release, or increased release of all three amines, but initially the effect of the catecholamines would mask that of the released 5-HT. This could simply be due to the fact that the amount

of at least one of the two catecholamines, noradrenaline, available for release is so much greater than that of 5-HT, since the concentration of noradrenaline in the hypothalamus is known to be several times higher than that of either 5-HT or adrenaline (Vogt, 1954; Amin, Crawford & Gaddum, 1954).

The effect of 5-HT should become apparent only some time later when the release, or increased release, of the amines ceases, because, as shown previously, the hyperthermic effect of intraventricular 5-HT lasts for many hours and is of longer duration than the hypothermic effect of intraventricular adrenaline or noradrenaline. The 5-HT could thus be responsible for the return of the temperature to normal or for the rise of temperature beyond the pre-injection level as well as for the shivering.

The difference between the action of pentobarbitone sodium and chloralose could be accounted for in one of the following ways without requiring a fundamental difference in the action of the two anaesthetics on the hypothalamus. Either pentobarbitone sodium is somewhat more potent in releasing 5-HT than chloralose; or when the effect of pentobarbitone on the hypothalamus wears off the release of 5-HT outlasts that of the catecholamines whereas this does not happen with chloralose; or the effect of chloralose on the hypothalamus wears off more gradually than that of pentobarbitone sodium. With the last two alternatives the difference between the two anaesthetics would occur only when their effect on the hypothalamus wears off. Any of these alternatives could account for the observed difference between the two anaesthetics. The ease with which fever is obtained following intraventricular injections of small doses of pentobarbitone favours the last alternative.

The present purely pharmacological experiments neither prove nor disprove these ideas. To prove them it is necessary to demonstrate the release of the amines during the changes in temperature seen in anaesthesia. Provided the amines released in the hypothalamus pass into the cerebral ventricles, this should not be too difficult, because the ventricles can be perfused in anaesthesia and the effluent then assayed for its content of 5-HT and catecholamines.

SUMMARY

1. In cats anaesthetized with pentobarbitone sodium or chloralose, body temperature is recorded rectally, and bacterial pyrogens, 5-hydroxytryptamine (5-HT), adrenaline and noradrenaline are injected into the cerebral ventricles through an indwelling cannula to determine whether the hypothalamus retains its reactivity to these substances under anaesthesia.

2. When cats are kept at room temperature (21–24° C) and not warmed by external heat, anaesthetic doses of intraperitoneal pentobarbitone

sodium or intravenous chloralose produce a profound fall in temperature lasting several hours. With chloralose the degree and duration of hyperthermia were shown to increase with dosage.

3. An intraventricular injection of 0·1 ml. 1/1000 typhoid vaccine, of 30 ng *Shigella dysenteria*, or of 200 μg 5-HT during a pentobarbitone sodium or chloralose anaesthesia, at a time when temperature has fallen to a low level, accelerates the return to normal temperature and then produces fever. The rise in temperature produced by the bacterial pyrogens begins after a latency of about 1 hr, whereas that produced by 5-HT after a latency of only a few minutes. An intraventricular injection of 50 μg adrenaline or noradrenaline, on the other hand, postpones the return to normal temperature for several hours.

4. The fall in temperature during anaesthesia can be attributed to an effect of the anaesthetics on the hypothalamus because, when injected intraventricularly in doses far too small to be effective on systemic application, both chloralose (less than 1 mg) and pentobarbitone sodium (3 mg) produce a fall.

5. The sole effect of chloralose on temperature is a fall; with pentobarbitone sodium there may be a fall followed by a rise beyond the level existing before the pentobarbitone sodium injection. This occurs when small doses are injected intraventricularly or when anaesthetic doses are injected intraperitoneally during fever produced by bacterial pyrogens.

6. On the assumption that temperature regulation in the hypothalamus is brought about by the release of 5-HT, adrenaline and noradrenaline, which occur naturally in the hypothalamus, the fall in temperature which occurs in anaesthesia as well as the differences in the changes of temperature observed between pentobarbitone sodium and chloralose anaesthesia cannot be due to the hypothalamus having become insensitive to the action of these three amines. In order to explain the changes in temperature during anaesthesia in the light of the new concept, it is necessary to assume that the anaesthetics modify the release of the amines. Possible ways in which the release may be influenced by the anaesthetics are discussed.

REFERENCES

Amin, A. N., Crawford, T. B. B. & Gaddum, J. H. (1954). The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol.* **126**, 596–618.

Canal, N. & Ornesi, A. (1961). La serotonina quale agente ipertermizzante. *Atti Accad. med. lomb.* **16**, 64–69.

Domer, F. R. & Feldberg, W. (1960). Tremor in cats: the effect of administration of drugs into the cerebral ventricles. *Brit. J. Pharmacol.* **15**, 578–587.

Feldberg, W. (1957). Anaesthesia and sleep-like conditions produced by injections into the cerebral ventricles of the cat. *J. Physiol.* **140**, 20–21 *P*.

Feldberg, W. (1959). A physiological approach to the problem of general anaesthesia and loss of consciousness. *Brit. med. J.* **ii**, 771–782.

FELDBERG, W. & MYERS, R. D. (1963). A new concept of temperature regulation by amines in the hypothalamus. *Nature, Lond.*, **200**, 1325.

FELDBERG, W. & MYERS, R. D. (1964). Effects on temperature of amines injected into the cerebral ventricles: a new concept of temperature regulation. *J. Physiol.* **173**, 226–237.

FELDBERG, W. & SHERWOOD, S. L. (1954). Injections of drugs into the lateral ventricle of the cat. *J. Physiol.* **123**, 148–167.

HUMPHREY, J. H. & BANGHAM, D. R. (1959). International Pyrogens Reference Preparations. *Bull. World Hlth Org.* **20**, 1241–1244.

VOGT, M. (1954). The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J. Physiol.* **123**, 451–481.