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EFFECTS ON TEMPERATURE OF AMINES INJECTED INTO THE CEREBRAL VENTRICLES. A NEW CONCEPT OF TEMPERATURE REGULATION

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The present experiments deal with a new central action of adrenaline, noradrenaline and 5-hydroxytryptamine (5-HT). They show that these amines affect body temperature when injected into the cerebral ventricles of an unanaesthetized cat. 5-Hydroxytryptamine raises the body temperature, whereas adrenaline and noradrenaline have the opposite effect and lower it, particularly when it is elevated by either 5-HT or pyrogens similarly applied. These findings suggest that the three amines which are present in relatively high concentrations in the hypothalamus (Vogt, 1954; Amin, Crawford & Gaddum, 1954) play a role in the hypothalamic regulation of body temperature.

The experiments are the outcome of two independent observations, the first of which is concerned with pyrogens and the second with the amines 5-HT, adrenaline, and noradrenaline. Pyrogens injected into the cerebral ventricles of a cat cause long-lasting fever and shivering. When the amines are similarly injected 5-HT produces shivering, whereas adrenaline and noradrenaline abolish drug-induced shivering.

Petersdorf & Bennett (1959) produced fever by the injection of pyrogens into the cisterna magna of rabbits. Fever produced in cats by the injection of pyrogens into the cerebral ventricles through an indwelling cannula has been described by Sheth & Borison (1960) as well as by Villablanca & Myers (1963), who in addition noted that shivering occurred. The effects, which were obtained with doses of pyrogen too small to be effective on intravenous injection, occurred after a latency of about 1 hr, and the body temperature remained elevated for many hours. According to Villablanca & Myers, the pyrogens act on the anterior hypothalamus reached from the third ventricle, because when they injected the pyrogens directly into this region fever and shivering occurred. On the other hand, the effect did not

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occur when the pyrogens were applied to various other regions of the hypothalamus.

The shivering produced by intraventricularly injected 5-HT as well as the anti-tremor or anti-shivering effect of intraventricularly injected adrenaline and noradrenaline have been observed in anaesthetized and unanaesthetized cats. Small amounts of the catecholamines injected into, or perfused through the cerebral ventricles were found to abolish tremor or shivering produced by intraperitoneal pentobarbitone sodium, by intramuscular chlorpromazine, or by tubocurarine injected into, or perfused through the cerebral ventricles. It could be shown that for the tubocurarine to produce shivering it had to pass through that part of the third ventricle which lies ventral to the massa intermedia, the walls of this part being formed by the hypothalamus. The 5-HT as well as the catecholamines probably also act on this structure when producing or abolishing shivering (Feldberg & Malcolm, 1959; Domer & Feldberg, 1960; Carmichael, Feldberg & Fleischhauer, 1962; Feldberg, 1963).

METHODS

In cats weighing 2·6–3 kg a Collison cannula was aseptically implanted under pentobarbitone sodium anaesthesia into the left lateral ventricle as originally described by Feldberg & Sherwood (1953, 1954), and with the modifications given by Carmichael, Feldberg & Fleischhauer (1964). After an interval of at least one week the cats were used for experiments at weekly intervals. All injections were made through the indwelling cannula without anaesthesia. During the experiments the cats were housed in wire-mesh cages to which they were accustomed. The dimensions of the cages were 100 cm × 45 cm × 53 cm. The temperature of the room varied between 20·5 and 22·5° C. Usually the cats were not fed for 24 hr before the experiment.

The temperature of the cats was measured by a thermistor probe inserted 10–12 cm into the rectum and held in position by adhesive tape affixed to the tube of the probe and gently wrapped around the root of the tail. The temperature was monitored continuously by a Kent multi-channel recorder calibrated from 37 to 42° C. The figures reproduced in this paper are plotted directly from the tracings obtained in this way.

Substances injected into the cerebral ventricles. Two pyrogens were used: (*a*) Typhoid AB vaccine (Burroughs Wellcome & Co. London) which contains *Salmonella typhi* and *paratyphi*, and (*b*) *Shigella dysenteriae*, somatic type D, from the World Health Organisation pyrogen standard (Humphrey & Bangham, 1959). Adrenaline bitartrate (B.D.H.), noradrenaline bitartrate (Bayer Products), and 5-HT creatinine sulphate (Roche Products Ltd.) were used. In order to exclude the possibility of contamination of the 5-HT creatinine sulphate with bacterial pyrogens a sample was sterilized and dialysed. The results obtained with this sample were the same as with the untreated salt. Creatinine sulphate was prepared from creatinine (B.D.H.) by treatment with a slight excess of sulphuric acid and the salt was then recrystallized. The values for the amines given in the text refer to the salts. All substances were dissolved or diluted in pyrogen-free 0·9 % NaCl solution, and the syringes, needles and all glass-ware used were rendered pyrogen-free by standard heating procedures. The pyrogens and the amines were injected in a volume of 0·1 ml. followed by an injection of 0·05 ml. 0·9% NaCl solution.

RESULTS

Adrenaline and noradrenaline on normal temperature

In previous experiments (Feldberg & Myers, 1963) adrenaline and noradrenaline injected intraventricularly in amounts of 50–100 μg were found to produce no fall in temperature. This led to the conclusion that the catecholamines reduce temperature only when it is elevated. These results, however, were obtained from one cat, and subsequent experiments on this cat showed that the usual fever produced by intraventricular injection of pyrogens (see later) was also absent. The injected fluid had probably not passed into that part of the third ventricle lying ventral to the massa intermedia. This is known to happen in some cats.

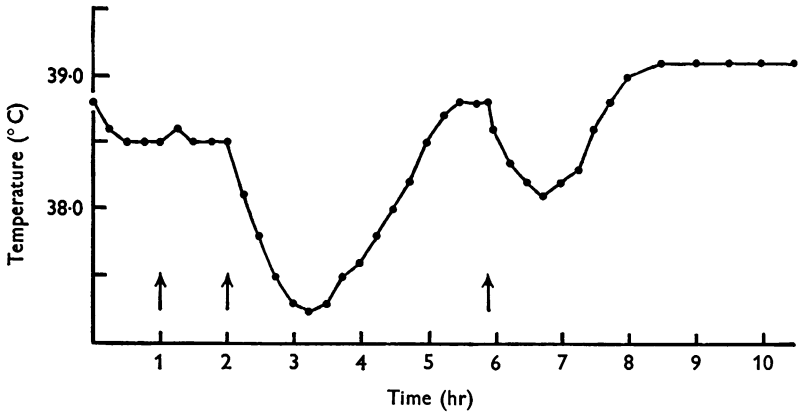

Fig. 1. Record of rectal temperature of an unanaesthetized cat. The arrows indicate injections into the cerebral ventricles of 0·1 ml. 0·9 % NaCl (1st arrow), 50 μg adrenaline (2nd arrow) and 50 μg noradrenaline (3rd arrow).

In the present experiments on a number of cats, both adrenaline and noradrenaline injected intraventricularly in amounts of 50–100 μg have always produced a fall in rectal temperature, usually of between 0·5 and 1° C, but, in a few instances, amounting to 1·3° C. A typical experiment showing the effects of intraventricular injections of 50 μg adrenaline and noradrenaline is illustrated in Fig. 1. Within a few minutes of the injections of the catecholamines the temperature begins to fall, reaches its lowest level within about an hour, may stay at this level for about half-an-hour and then rises during the next 1½–2 hr to a temperature often somewhat higher than the pre-injection level. During the fall of temperature the ear vessels dilate, the pinnae feel warm and appear pink when viewed from the inner side. During the rise in temperature the ear vessels contract again, and there may be light shivering of the flanks and trunk.

In most experiments, 50 μg adrenaline produced almost as great an effect as 100 μg noradrenaline, which suggests that adrenaline is nearly twice as effective as noradrenaline. It is difficult, however, to make a more accurate comparison, because the effects vary in different cats, and the second injection of a given dose of either adrenaline or noradrenaline is often less effective than the first.

Adrenaline and noradrenaline during pyrogen fever

Both typhoid vaccine and *Shigella dysenteriae* produce a long-lasting elevation of rectal temperature when injected through an indwelling cannula into the cerebral ventricles of an unanaesthetized cat. The main rise occurs after a latency of about an hour during which time there may be a small transient rise. Typical fever responses to the injection of typhoid vaccine in a dilution 1/1000 and of 30 ng *Shigella dysenteriae* are shown in Fig. 2 *A* and *B*. During the rising phase as well as during the period of elevated temperature the cat often shivers either continuously or in bursts. From the onset of the rise in temperature and throughout the period of fever, the cat usually lies in the cage with its eyes closed giving the appearance of being asleep. The ear vessels are constricted, the pinnae feel cold and look pale when viewed from the inner side.

Adrenaline or noradrenaline injected into the cerebral ventricles during the pyrogen fever causes a lowering of rectal temperature and cessation of shivering. Greater falls of temperature are obtained with the catecholamines when they are injected during pyrogen fever than at normal temperature.

In Fig. 2, the changes in rectal temperature following 25 μg in one (*A*) and 50 μg adrenaline in another cat (*B*) are illustrated. In both cats the first injection is given whilst the temperature is still rising. The rise ceases almost immediately and within a few minutes the temperature begins to fall and drops about 1·5° C within 1 hr; it then rises again to fever level. During the fall and until the time the temperature rises again shivering ceases. The ear vessels are dilated, the pinnae feel warm and appear pink when viewed from the inner side. In both experiments the second injection of adrenaline is less effective in lowering the temperature than the first, although this is not always the case. Given long after the pyrogen fever has been in progress, adrenaline is as effective in reducing the high temperature as when injected during the early part of the fever. The same is true for noradrenaline. Figure 3 *A* illustrates responses to 40 and 100 μg injected into the cerebral ventricles during the rising phase of fever produced by typhoid vaccine similarly injected. The 40 μg lower the temperature by about half a degree, whereas after the injection of 100 μg temperature it falls from 40·3 to 37·9° C, i.e. by 2·4° C in less than an hour, shivering

ceases and the vessels of the pinnae dilate. Figure 3*B* also shows that 100 μg noradrenaline is more potent than 50 μg adrenaline.

By spacing appropriately the intraventricular injections of small doses of noradrenaline, the pyrogen-produced fever is lowered over several hours. This is illustrated by the experiment shown in Fig. 3*C* in which 25 μg noradrenaline is injected at intervals of 15–30 min.

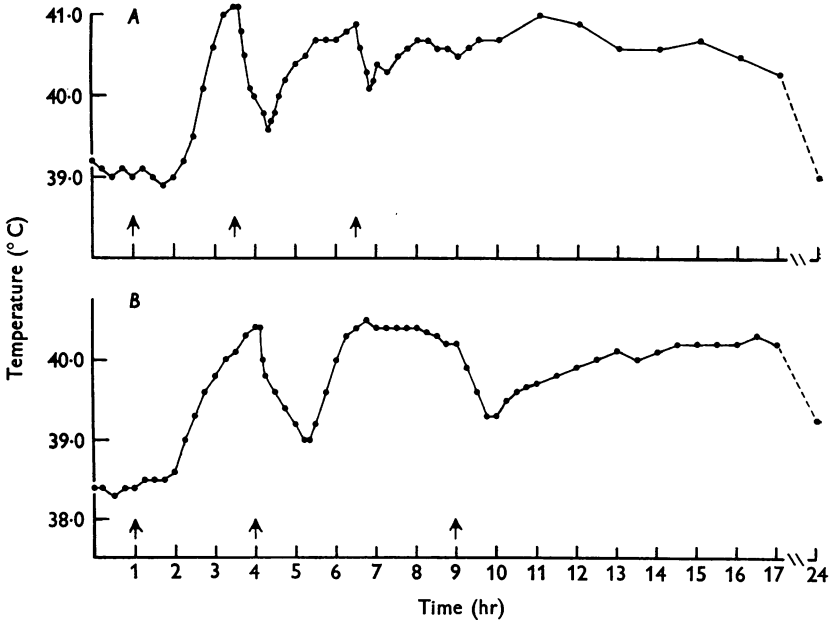

Fig. 2. Records of rectal temperature of two unanaesthetized cats. The arrows indicate injections into the cerebral ventricles; in record *A* of 0·1 ml. 1/1000 typhoid vaccine (1st arrow) and of 25 μg adrenaline (2nd and 3rd arrows) and in record *B* of 30 ng *Shigella dysenteriae* (1st arrow) and of 50 μg adrenaline (2nd and 3rd arrows).

5-HT on normal temperature and during pyrogen fever

The injection of 100–200 μg of 5-HT into the cerebral ventricles of an unanaesthetized cat causes a sustained elevation in rectal temperature. As shown in the two experiments of Fig. 4 the rise is biphasic. Within a few minutes of the injection the temperature begins to rise and continues to do so for about half-an-hour. The extent of the rise varies between 0·5 and 1·2° C. During the next hour there is a transitory decline of 0·5° C or even less, and the temperature may, therefore, either return to the pre-injection level (Fig. 4*A*) or remain partially elevated (Fig. 4*B*). There follows then a prolonged elevation of 1·5–3·0° C; up to 15 hr elapse before the temperature begins to return to normal. The rise in temperature is accompanied by

shivering and constriction of the ear vessels. Shivering is particularly intense during the initial rise, and continues intermittently in bursts as long as the temperature is rising. During the fever the cat lies quietly in the cage, usually with its eyes closed, giving the appearance of being asleep.

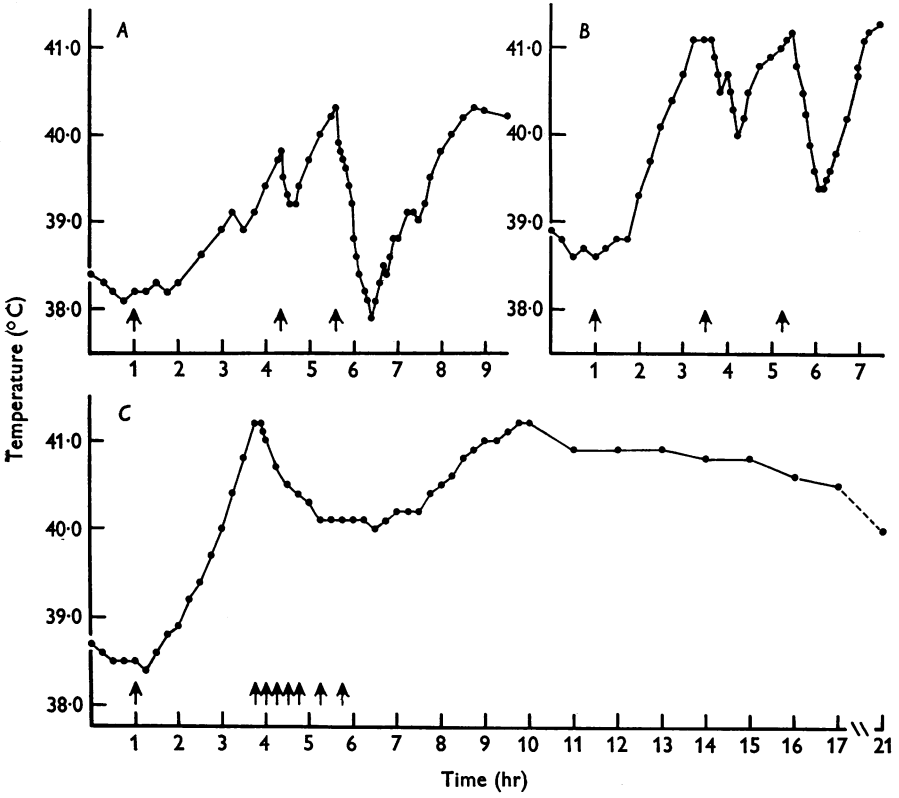

Fig. 3. Records of rectal temperature of two unanaesthetized cats. Records *B* and *C* were obtained from the same cat at one week's interval. The arrows indicate injections into the cerebral ventricles; in record *A* of 30 ng *Shigella dysenteriae* (1st arrow) and of 40 and 100 μg noradrenaline (2nd and 3rd arrows), in record *B* of 0·1 ml. 1/1000 typhoid vaccine (1st arrow), of 50 μg adrenaline (2nd arrow) and of 100 μg noradrenaline (3rd arrow) and in record *C* of 30 ng *Shigella dysenteriae* (1st arrow) and of 25 μg noradrenaline at 15 and 30 min intervals (at 2nd to 8th arrows).

The 5-HT is injected as the creatinine sulphate, and half of its weight is due to creatinine sulphate. The temperature elevation, however, is not an effect of the creatinine sulphate since this substance causes no rise in temperature when injected intraventricularly. This is illustrated in the experiment shown in Fig. 4*B* in which 100 μg of creatinine sulphate are injected 3 hr before the injection of 200 μg 5-HT.

The possibility that the second, long-lasting, elevation of temperature produced by intraventricular 5-HT is due to contamination of the substance with bacterial pyrogen is ruled out by the fact that 5-HT remains effective after sterilization and dialysis, which would remove any contamination with bacterial pyrogen. The record shown in Fig. 5*B* is in fact obtained with 5-HT treated in this way. The record is from the same cat from which the record shown in Fig. 4*B* was obtained with untreated 5-HT a week earlier.

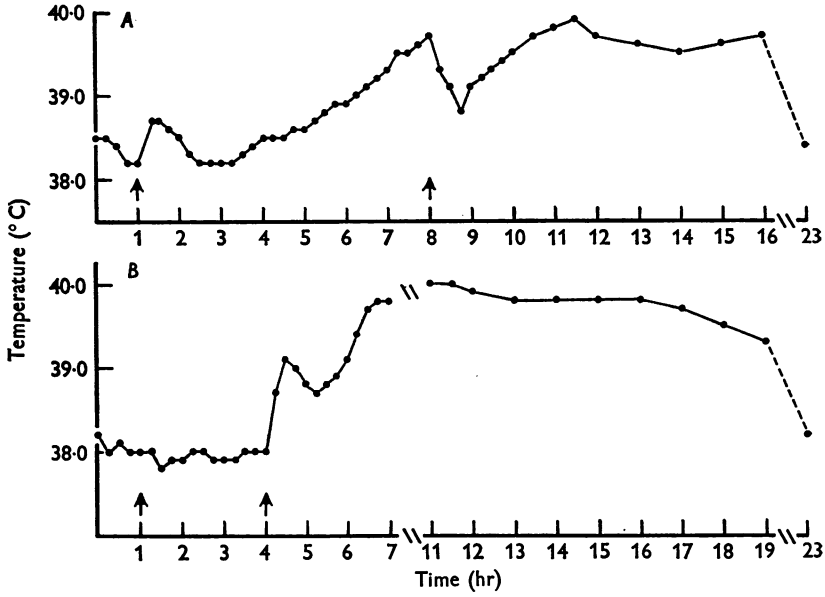

Fig. 4. Records of rectal temperature of an unanaesthetized cat. Record *B* obtained 2½ months after record *A*. The arrows indicate injections into the cerebral ventricles; in record *A* of 200 μg 5-HT (1st arrow) and of 100 μg noradrenaline (2nd arrow) and in record *B* of 100 μg creatinine sulphate (1st arrow) and of 200 μg 5-HT (2nd arrow).

When 5-HT is injected during a pyrogen fever it produces an additional steep rise and the high temperature is maintained for a longer period than it would have been by pyrogen or by 5-HT alone. In the experiment of Fig. 5*A*, 200 μg 5-HT are injected during the fever produced by typhoid vaccine with the result that the temperature rises from 40·1–41·1° C with ½ hr, and this high temperature, about 3° C above normal, continues for over 20 hr. In other experiments in which the rise is not interrupted by injections of catecholamines the fever is sometimes maintained for over 30 hr.

Adrenaline and noradrenaline during 5-HT fever

Both adrenaline and noradrenaline, injected intraventricularly, lower the temperature elevated by intraventricular 5-HT in the same way as they lower pyrogen fever. The effects of 100 μg noradrenaline and of 50 μg adrenaline are shown in Figs. 4 and 5.

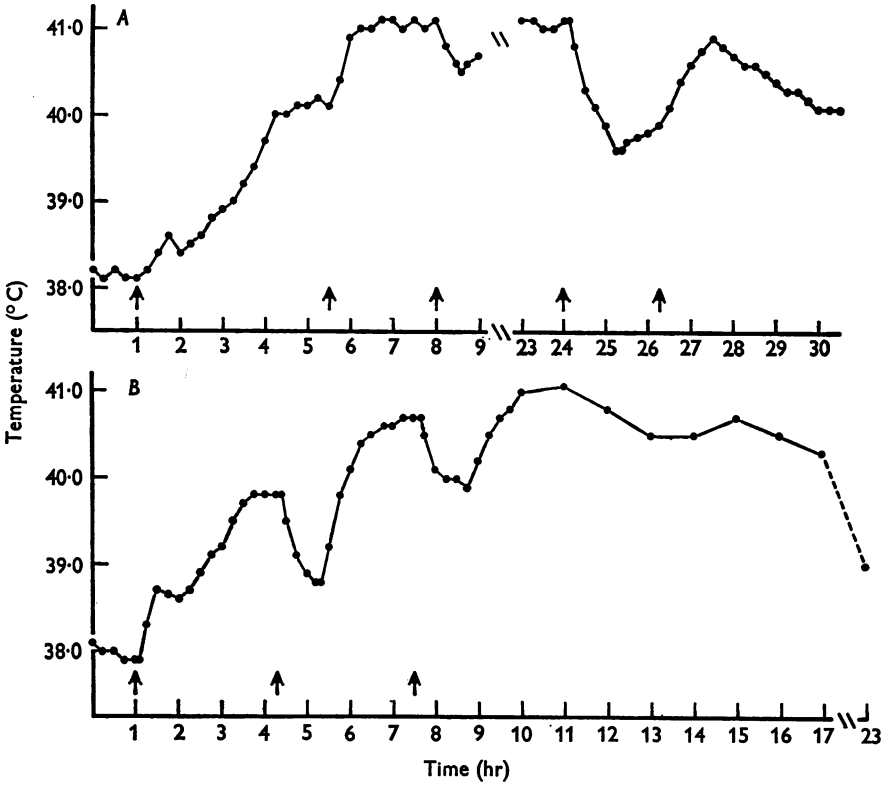

Fig. 5. Records of rectal temperature of two unanaesthetized cats. The arrows indicate injection into the cerebral ventricles; in record *A* of 0·1 ml. 1/1000 typhoid vaccine (1st arrow), of 200 μg 5-HT (2nd and 5th arrows), of 100 μg noradrenaline (3rd arrow) and of 50 μg adrenaline (4th arrow) and in record *B* of 200 μg dialysed 5-HT (1st arrow), of 50 μg adrenaline (2nd arrow) and 100 μg noradrenaline (3rd arrow).

During the prolonged fever due to a combination of pyrogen and 5-HT, the temperature appears to become particularly sensitive to the catecholamines. This is illustrated in Fig. 5*A* in which 50 μg adrenaline given 23 hr after the pyrogen and 19 hr after the 5-HT injection cause a greater and longer-lasting fall than 100 μg noradrenaline given 16 hr earlier.

DISCUSSION

The finding that we can influence rectal temperature by the injection of adrenaline, noradrenaline and 5-HT into the cerebral ventricles of unanaesthetized cats forms the basis of a new concept according to which body temperature is regulated by the release of these amines in the hypothalamus.

Adrenaline, noradrenaline and 5-HT occur naturally in the hypothalamus, and of the three, noradrenaline occurs in the highest concentration, i.e. about 1/1 million. This is of a different order of magnitude from the concentrations in which the amines are injected into the cerebral ventricles. When 200 μg is injected in a tenth of a millilitre the concentration is 1/500, and even 25 μg injected in this volume gives a concentration of 1/4000. This discrepancy, however, creates no difficulty. First, the injected amines are diluted by the c.s.f. in the cerebral ventricles. That in itself would not sufficiently narrow the gap. But it is not the concentration of the amines in the c.s.f. which is active, but the concentration present within the ventricular wall after the amines have passed the ependyma. This concentration may be only a fraction of that in the c.s.f. Moreover, the amines are unlikely to be evenly distributed throughout the hypothalamus so that their concentration in the cellular structures in which they are held, and from which they are released, may be much stronger than the over-all concentration of amines obtained on extraction of the hypothalamus.

The effects of the three amines on temperature are attributed to an action on the hypothalamus. This conclusion is based on the results of previous experiments described in the introduction, pertaining to the ability of the amines and other substances to evoke or abolish shivering when injected into or perfused through the cerebral ventricles of the cat. In these experiments it was shown that to produce the effects the substances had to irrigate that part of the third ventricle lying ventral to the massa intermedia. Further evidence has recently been provided by experiments in which the amines have been injected directly into the anterior hypothalamus. Injected in amounts of only 1–2 μg they produced the same changes in temperature as described in the present experiments (W. Feldberg & R. D. Myers, unpublished experiments).

There are two possible ways in which the amines may affect body temperature. They may be continuously released and the normal temperature may be the outcome of a fine balance between the release of 5-HT and of the catecholamines. Changes in temperature would then be brought about by a disturbance of this balance. Or, normal temperature is maintained independent of the release of the three amines, their release being the mechanism by which changes in temperature are effected.

A fall in temperature may therefore be visualized as being due to an augmentation in the release of the catecholamines together with inhibition of the release of 5-HT, or solely to an initiation of the release of the catecholamines. And a rise in temperature would be due to an augmentation in the release of 5-HT together with inhibition of the release of adrenaline and noradrenaline, or solely to an initiation of the release of 5-HT. The rise in temperature produced by bacterial pyrogens, i.e. the fever of infectious diseases, may be brought about in one of these ways. In addition, pyrogens may render the hypothalamus more sensitive to the action of 5-HT, and there is the further possibility that pyrogens do not act solely through the release of the hypothalamic amines, but mimic the effect of 5-HT.

Changes in temperature brought about by agents other than bacterial pyrogens must also be considered in the light of the new concept. Take, for instance, the antipyretics which counteract fever produced by bacterial pyrogens but do not lower normal temperature. On the assumption that bacterial pyrogens act by initiating the release of 5-HT and by rendering the appropriate hypothalamic structures hypersensitive to this amine, the action of the antipyretics would be to reverse these changes, and no effect on normal temperature would be expected. Or, if we take the other view, that bacterial pyrogens also inhibit the normal continuous release of catecholamines, the antipyretics would, in addition, restore this release and might even accentuate it. According to this view the antipyretics would in part act through the release of catecholamines. This, too, would be expected to have little or no effect on a temperature already kept down to a given level, the normal temperature, by the continuous release of the catecholamines. In this context it is interesting that in the present experiments the catecholamines usually did not lower normal temperature for more than 0·5–1° C when injected intraventricularly, whereas greater reductions were obtained when they were injected during fever. Even then, however, temperature was not lowered beyond the normal range.

If antipyretics act in part by the release of catecholamines in the hypothalamus, the fact that they share with the catecholamines another property, analgaesia, may be explained along similar lines. Antipyretics are analgaesics, and the catecholamines, too, exert analgaesic effects when acting from the liquor spaces (Bass, 1914; Leimdorfer & Metzner, 1949; Feldberg & Sherwood, 1954, 1957) when applied directly to the hypothalamus (Myers, 1964) or when given subcutaneously (Radouco-Thomas, Nosal, Radouco-Thomas & Le Breton, 1959).

A characteristic feature of the fever produced by intraventricular 5-HT is its long duration. It lasts up to 15 hr which is many times longer than the duration of the fall in temperature obtained with intraventricular

adrenaline or noradrenaline. Differences in the rate of enzymatic inactivation between 5-HT and the catecholamines after their penetration into the brain tissue could fully account for this difference in duration of the response. An intraventricular injection of bacterial pyrogens also produces such a long-lasting fever, whereas fever resulting from an intravenous injection of bacterial pyrogens lasts 1–3 hr. This would suggest that the bacterial pyrogens, after having penetrated and permeated the walls of the third ventricle, are protected against inactivation for a much longer period than when reaching the hypothalamus through the blood stream. Further, as long as they remain in this diencephalic structure, the pyrogens release 5-HT, render the appropriate cellular elements hypersensitive to this amine, and may also inhibit the release of the catecholamines.

There is evidence that the amines, by their action on the hypothalamus, affect body temperature through both heat production and heat elimination. The rise in temperature produced by 5-HT is associated with shivering and constriction of the vessels of the external ear; and the fall, produced by catecholamines, with cessation of shivering and dilatation of the ear vessels. It has also been shown (Carmichael *et al.* 1962) that the catecholamines, injected into the cerebral ventricles, reduce muscle tone. Whether in addition the amines influence heat production in the liver, or heat elimination by secretion from the sweat glands in the paws has not been examined.

To understand the way the hypothalamus regulates temperature we must know what goes on in this structure. We assume it is the release of the three amines, and although it is too early to discuss the mechanism of their release the new concept may finally be the means whereby temperature regulation is understood.

SUMMARY

1. In unanaesthetized cats, rectal temperature was continuously recorded by means of a thermistor probe inserted into the rectum. The changes in temperature were examined when 5-hydroxytryptamine (5-HT), adrenaline or noradrenaline were injected in a volume of 0·1 ml. into the lateral cerebral ventricle through a permanently implanted Collison cannula.

2. An intraventricular injection of 100–200 μg 5-HT raised the temperature whereas the injection of adrenaline or noradrenaline in amounts of 25 μg or more had the opposite effect and lowered the temperature, particularly when it had been elevated by either 5-HT or pyrogens similarly applied.

3. It is concluded that the effects of the three amines are on the hypothalamus in which they occur naturally in relatively high concentrations,

and the concept is put forward that temperature regulation is mediated through the release of these amines in the hypothalamus.

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