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BODY TEMPERATURE RESPONSES IN CATS AND RABBITS TO THE MONOAMINE OXIDASE INHIBITOR TRANYLCYPROMINE

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SUMMARY

1. In unanaesthetized cats tranylcypromine (1–10 mg/kg) had scarcely any effect on rectal temperature when injected intraperitoneally, yet such injections prevented the deep and long-lasting fall in rectal temperature which normally occurs when the cat is anaesthetized by intraperitoneal pentobarbitone sodium or intravenous chloralose. The anaesthesia itself, however, was not affected. In some of the experiments with pentobarbitone sodium rectal temperature even rose to fever level.

2. In anaesthetized as well as in unanaesthetized cats injections of tranylcypromine (0·1–1 mg) into the cerebral ventricles caused a rise in rectal temperature.

3. In rabbits, rectal temperature was scarcely affected when surgical anaesthesia was produced by intravenous infusions of pentobarbitone sodium under the same condition in which, in cats, intraperitoneal pentobarbitone sodium produced a deep and long-lasting fall in temperature, i.e. when no external heat was applied but excessive dissipation of heat was prevented by placing the rabbit on a cotton-wool pad. However, when it was placed on the metal surface of an operating table, the anaesthesia was associated with a deep fall in rectal temperature.

5. In anaesthetized and unanaesthetized rabbits tranylcypromine had no effect on rectal temperature when injected intraperitoneally (10 mg/kg) or into the cerebral ventricles (1 mg).

5. These results are discussed in relation to the theory that the three monoamines in the hypothalamus, 5–hydroxytryptamine (5-HT), adrenaline and noradrenaline, act as central transmitters in temperature regulation.

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INTRODUCTION

The present experiments are concerned with the theory that the three monoamines in the hypothalamus, 5-HT, adrenaline and noradrenaline, act as central transmitters in temperature regulation. The experiments deal with the effect on body temperature of tranylcypromine injected intraperitoneally or into the cannulated cerebral ventricles of unanaesthetized and anaesthetized cats and rabbits, and are a continuation of recent work in which it was shown that tranylcypromine increased the 5-HT output from the perfused third ventricle of anaesthetized cats and that this increase was associated with a rise in rectal temperature (El Hawary, Feldberg & Lotti, 1966).

When acting on the hypothalamus, the effect of the monoamines is different in cats from that in rabbits. In cats 5-HT raises and the catecholamines lower body temperature (Feldberg & Myers, 1964*a*, 1965), whereas in rabbits the catecholamines raise body temperature and 5-HT has a weak hypothermic effect (Cooper, Cranston & Honour, 1965). Further, the substrate for the monoamine oxidase of the brain appears to be different in cats from that in rabbits, for in cats the brain level of 5-HT alone, but in rabbits that of the catecholamines as well, increases after administration of inhibitors of monoamine oxidase (Vogt, 1959; Spector, Shore & Brodie, 1960; Pscheidt, Morpurgo & Himwich, 1962; Spector, 1963). The question therefore arises as to whether inhibition of the monoamine oxidase in the hypothalamus would have a different effect on body temperature in cats than in rabbits. And further, whether differences in the temperature response between the two species would be revealed by examining the effect of tranylcypromine not only in the unanaesthetized but also in the anaesthetized animal, because anaesthetics are thought to modify the release of the monoamines in the hypothalamus.

METHODS

The experiments were done on cats of either sex and on female rabbits weighing between 2·8 and 3·4 kg. For anaesthetizing the cats intraperitoneal pentobarbitone sodium (30–33 mg/kg) or intravenous chloralose (50–55 mg/kg) was used. The chloralose was injected into a saphenous vein under anaesthesia induced with ethyl chloride, the vein being exposed by a small aseptic skin incision which was afterwards closed by a single stitch. For anaesthetizing the rabbit, pentobarbitone sodium (25 mg/kg) was infused slowly (over about 2 min) into a marginal ear vein. For the infusion the vein was cannulated with polythene tubing (20 gauge) filled with pyrogen-free solution of 1 % heparin in 0·9 % NaCl, the tubing being kept in position throughout the experiment so as to permit further infusions of pentobarbitone sodium when anaesthesia lightened. Following each infusion the pentobarbitone sodium in the tubing was washed in with the heparin saline solution and its free end was then stoppered with a sterile pin.

Rectal temperature was measured by a thermistor probe inserted about 10 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. The figures reproduced in this paper are plotted directly from the tracings obtained in this way. The unanaesthetized animals were kept in their cages, the floor of which was covered with straw. The anaesthetized animals, if not otherwise stated, were placed on a cotton-wool pad; usually they were lying on their sides.

For injection of drugs into the cerebral ventricles a Collison cannula was aseptically implanted under pentobarbitone sodium anaesthesia into the left lateral ventricle as originally described by Feldberg & Sherwood (1953) and with the modifications given by Carmichael, Feldberg & Fleischhauer (1964). In the experiments on rabbits the cannula was anchored to the skull by three small stainless-steel screws inserted into the skull around the cannula and joined to it by dental cement. At least 1 week was allowed for recovery before intraventricular injections of drugs were made in a volume of 0·1 ml. and washed in by 0·05 ml. 0·9 % NaCl solution.

In a few experiments the third ventricle of anaesthetized cats was perfused with artificial c.s.f. from a cannula inserted into the third ventricle with its opening ventral to the massa intermedia, and the outflow was collected from the cannulated aqueduct. The method of perfusion has been described and illustrated elsewhere (Feldberg & Myers, 1966). The outflow was assayed for 5–HT on the fundus strip of the rat's stomach suspended in a 5 ml. bath according to the method described by Vane (1957).

In another few experiments on anaesthetized cats, arterial blood pressure and respiration were recorded, the blood pressure from the cannulated right femoral artery with a 'Bell–Howell' pressure transducer, respiration through the tracheal cannula with a Grass Volumetric Pressure Transducer, both coupled to an Offner dynograph.

Drugs used. The monoamine oxidase inhibitor tranylcypromine sulphate was kindly supplied to us by Dr P. Hey, of Smith Kline & French. The 5–HT used was the creatinine sulphate, the noradrenaline the bitartrate. The amounts injected either intraperitoneally or intraventricularly refer to the salts, the amounts of 5–HT assayed in the effluent from the perfused third ventricle to the base.

RESULTS

Experiments on cats

Intraperitoneal injections of tranylcypromine. An intraperitoneal injection of 10 mg/kg tranylcypromine into an unanaesthetized cat produced licking movements, profuse salivation and tachypnoea. The ears became cold and the eyes opened wide. The cat appeared to become more excitable and more alert, and gave the impression of being apprehensive. Two cats hissed when the door of the cage was opened and an attempt was made to touch them. In some cats, retching and vomiting occurred. Shivering was not observed.

The first effect which occurred within a few minutes of the injection was the licking movements, which increased in frequency and were followed by profuse salivation, which lasted for several hours. The rate of respiration began to increase within 15 min, reached up to 150/min within an hour, and remained accelerated for a few hours.

With 2·5 mg/kg, licking movements, salivation and tachypnoea also

occurred. The ears became cold and the eyes opened wide, but the effects did not last as long as with the larger dose, and the rate of respiration did not increase to more than 100/min. With 1 mg/kg no definite effects were observed, except that vomiting occurred in one cat as late as 2 hr after the injection.

The effect of intraperitoneal tranylcypromine on rectal temperature is shown for different doses in Fig. 1. With 10 mg/kg there was a small rise which in one cat (*A*) amounted to 1° C, and in another, (*B*), to 0·4° C. Smaller doses of tranylcypromine had no consistent effect on temperature (see cats *C*, *D* and *E*).

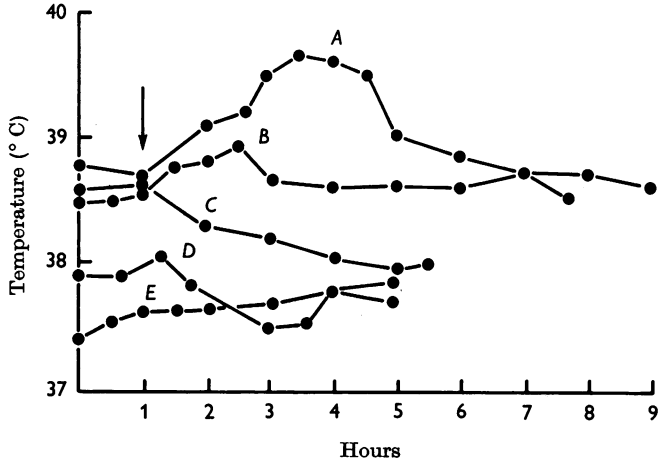

Fig. 1. Records of rectal temperature from five unanaesthetized cats. At the arrow, intraperitoneal injection of tranylcypromine. Cats *A* and *B*, 10 mg/kg; cats *D* and *E*, 2·5 mg/kg; cat *C*, 1 mg/kg.

Several of the effects obtained in unanaesthetized cats were evident also in cats anaesthetized with intraperitoneal pentobarbitone sodium or intravenous chloralose. In pentobarbitone as well as in chloralose anaesthesia, the ears are warm, the eyes closed, the pupils narrow, sometimes slit-like, and the nictitating membranes are protruded. There is a gradual slowing of respiration and heart rate, and the muscle tone is low. However, when the anaesthetic was given 15 min after an intraperitoneal injection of 2·5 or 10 mg/kg tranylcypromine, the ears became cold, the eyes opened wide, the pupils gradually dilated, the nictitating membranes remained withdrawn, and the heart rate increased. The previously regular respiration was interrupted from time to time by deep sigh-like breaths, otherwise respiratory rate increased slightly, or was not affected. There was an increase in muscle tone after the larger dose of tranylcypromine but

shivering was not always present. Vomiting and salivation were not encountered.

In one cat anaesthetized with pentobarbitone sodium arterial blood pressure and heart rate were recorded. The blood pressure began to rise 15 sec after the intraperitoneal injection of tranylcypromine (10 mg/kg), reached a maximum within 3 min and then began to fall, and continued to fall gradually during the next 2 hr. The heart rate rose from 210 to 265/min, but initially, whilst the blood pressure was rising, there was a transitory reduction to 200/min. Two hours after the injection the heart rate was still 245/min.

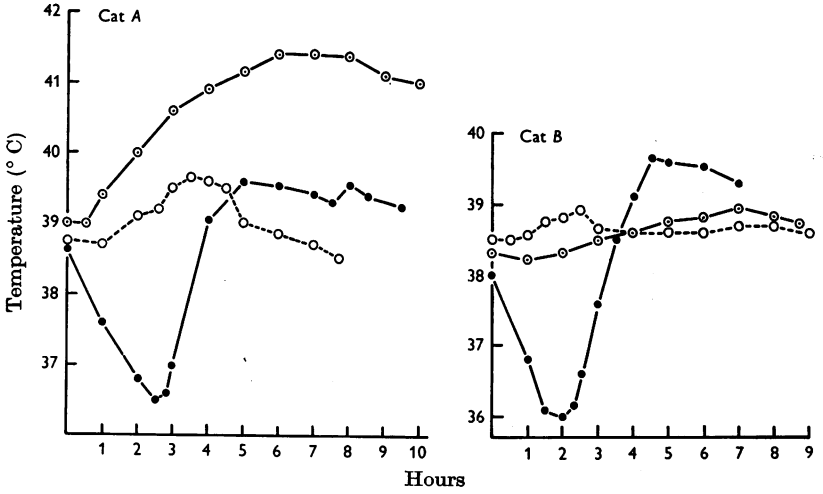

Fig. 2. Records of rectal temperature from two cats. The three temperature curves from each cat were obtained at intervals of at least 1 week. (○ - - - - ○), Intraperitoneal injection of tranylcypromine (10 mg/kg), 1 hr after beginning of records. Same temperature curves as those in Fig. 1 for cats *A* and *B*. (●——●), Intraperitoneal injection of pentobarbitone sodium (30 mg/kg) 15 min before beginning of records. (⊙——⊙), Intraperitoneal injection of tranylcypromine (10 mg/kg) 30 min, and of pentobarbitone sodium (30 mg/kg) 15 min, before beginning of records.

Although in unanaesthetized cats intraperitoneal tranylcypromine had little effect on rectal temperature, it prevented the steep and long-lasting fall in temperature produced by anaesthetizing doses of pentobarbitone sodium or chloralose, yet the cats became fully anaesthetized. After tranylcypromine an injection of pentobarbitone sodium sometimes even produced fever.

Results obtained when pentobarbitone sodium was injected intraperitoneally after the tranylcypromine are illustrated in Figs. 2 and 3.

From each cat three temperature curves were obtained at intervals of at least 1 week. The curves with the open circles are the same as shown in Fig. 1 for cats *A*, *B* and *D*.

In cat *A*, Fig. 2, tranylcypromine (10 mg/kg) alone had caused a rise in rectal temperature of 1° C, pentobarbitone sodium alone a fall of over 2° C, but when the pentobarbitone sodium was injected 15 min after the tranylcypromine this fall was replaced by a rise of nearly 2·5° to 41·5° C. More usual was the type of result obtained in cat *B*, Fig. 2, in which the fall produced by the pentobarbitone sodium was prevented, but not converted into a rise by the tranylcypromine injection.

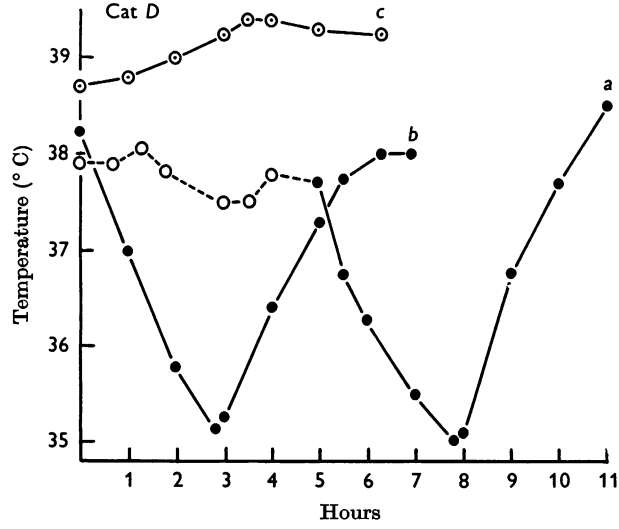

Fig. 3. Records of rectal temperature from one cat. The three temperature curves were obtained at intervals of at least 1 week. Record *a* (○ - - - - ○), intraperitoneal injection of tranylcypromine (2·5 mg/kg) 1 hr after beginning of record (same temperature curve as in Fig. 1 (for cat *D*) followed after 4 hr (●——●) by intraperitoneal injection of pentobarbitone sodium (30 mg/kg). Record *b* (●——●), intraperitoneal injection of pentobarbitone sodium (30 mg/kg) 15 min before beginning of record. Record *c* (⊙——⊙), intraperitoneal injection of tranylcypromine (2·5 mg/kg) 30 min, and of pentobarbitone sodium (30 mg/kg) 15 min, before beginning of record.

The tranylcypromine was also effective in smaller doses. This is shown in Fig. 3. The injection of 2·5 mg/kg tranylcypromine alone produced a fall of 0·5° C (first half of record *a*), the injection of pentobarbitone sodium alone a fall of 3° C (record *b*), but when the pentobarbitone sodium was given 15 min after the tranylcypromine, temperature rose 0·7° C (record *c*). This experiment also illustrates that the effect of tranylcypromine was no

longer obtained after 4 hr, when pentobarbitone sodium again produced its hypothermic action (second half of record *a*).

Intraperitoneal tranylcypromine exerted its effect on rectal temperature not only when injected before, but also when injected during, pentobarbitone sodium anaesthesia. When given during the falling phase of temperature it either stopped the fall, or, as illustrated by the two experiments of Fig. 4, it caused a rise. The upper record shows the effect of 2·5 mg/kg, the lower of 1 mg/kg, tranylcypromine injected (at the arrow) 1½ hr after the

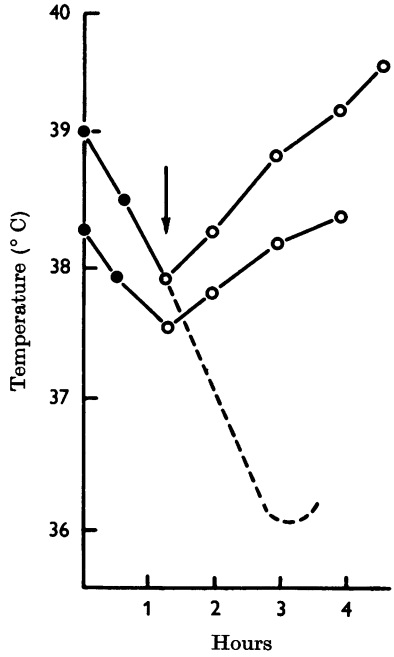

Fig. 4. Records of rectal temperature from two cats. The two temperature curves begin 15 min after an intraperitoneal injection of pentobarbitone sodium (30 mg/kg). At the arrow, intraperitoneal injection of tranylcypromine (2·5 mg/kg, upper record, and 1 mg/kg, lower record). The interrupted line of the upper record shows the continuation of the fall in temperature obtained in the same cat with pentobarbitone sodium (30 mg/kg) alone. Upper temperature curve obtained from cat *B*, lower from cat *C*, of Fig. 1.

pentobarbitone sodium. The interrupted line indicates how, in the same cat, temperature continued to fall when no tranylcypromine had been injected. The lower record was obtained from cat *C* of Fig. 1, in which the injection of 1 mg/kg tranylcypromine into the anaesthetized cat had produced a fall of 0·7° C. Smaller doses than 1 mg/kg were not tested because even 1 mg/kg was not always effective; in one cat, for instance, two

such injections had to be given to stop the fall in temperature produced by the pentobarbitone sodium.

The result obtained with chloralose injected intravenously 15 min after an intraperitoneal injection of tranylcypromine is illustrated in Fig. 5. The cat was particularly sensitive to the chloralose. Temperature fell from 39 to 28° C and did not return to normal within 15 hr as shown by the curve with the filled circles. The cat was still anaesthetized after 24 hr. When 10 days later the injection of chloralose was preceded by an injection of tranylcypromine (10 mg/kg) the chloralose produced an equally

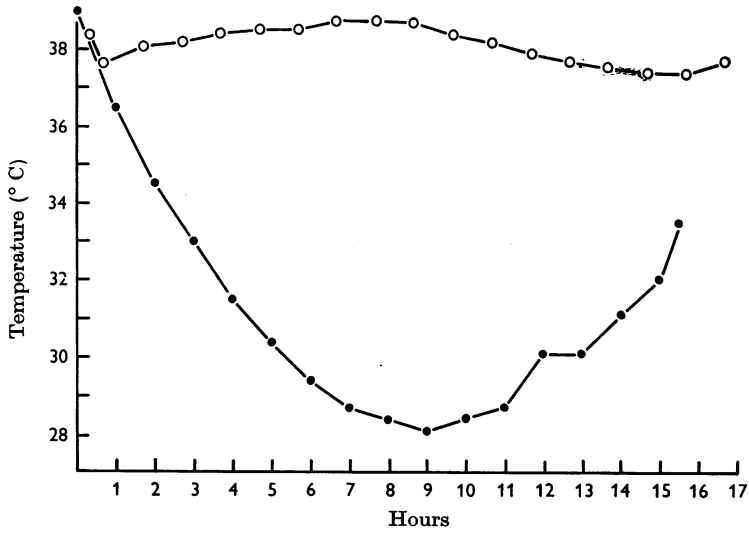

Fig. 5. Records of rectal temperature from one cat. The two temperature curves were obtained at an interval of 10 days and begin about 10 min after an intravenous injection of chloralose (50 mg/kg) ●——●, chloralose alone; ○——○, intraperitoneal injection of tranylcypromine given 15 min before chloralose.

long-lasting anaesthesia; temperature, however, did not fall, as shown by the curve with the open circles.

Smaller doses of tranylcypromine (5 or 2·5 mg/kg) did not always prevent the fall in temperature produced by the chloralose, but sometimes only attenuated it. For instance, in one cat the injection of 5 mg/kg reduced the fall by 20 %, whereas in another 2·5 mg/kg was sufficient to prevent it.

In previous experiments on cats anaesthetized with pentobarbitone sodium, it was shown that the 5-HT output from the perfused third ventricle increased on intraperitoneal injection of tranylcypromine and that this increase was associated with a rise in temperature (El Hawary *et al.* 1966). A similar result has been obtained in chloralose anaesthesia, as

illustrated in Fig. 6. In this experiment the 5-HT output was 0·7 ng/ml. in the two-20 min samples collected before the injection of tranylcypromine (5 mg/kg); after its injection the output rose to 5 ng/ml. and the previously falling temperature began to rise.

Intraventricular injections of tranylcypromine. An intraventricular injection of 0·5 mg of tranylcypromine into unanaesthetized cats produced within a few minutes licking movements, miaowing and mild piloerection

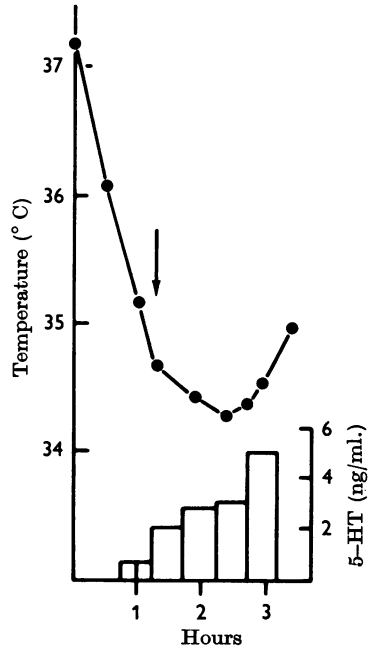

Fig. 6. Record of rectal temperature from a cat anaesthetized with intravenous chloralose (50 mg/kg). Third ventricle perfused with artificial c.s.f. at a rate of 0·05 ml./min; collection of effluent for the assay of 5–HT began about 1 hr after the onset of anaesthesia. The block diagram below the temperature curve represents 5–HT output in ng/ml. of effluent. At the arrow, intraperitoneal injection of tranylcypromine (5 mg/kg).

on the back. The ears became warm but later, after 30–90 min, turned cold. One of the earliest effects was shivering. At first it was short-lasting, and stopped as the ears became warm, but reappeared as they turned cold, and then it continued at varying intensity during the following hours, periods of vigorous shivering being interrupted by periods of mild shivering, or no shivering at all. Respiration became quicker, but the rate did not increase to more than 85/min. Within an hour or two of the injection the cat became sleepy, its eyes closed, it curled up and did not react, or only

a little, to sudden loud noises. This condition persisted for several hours. One cat retched and vomited 3 min after the injection.

The intraventricular injection of a smaller dose of tranylcypromine (0·1 mg) produced very much the same effects except that the warming of the ears did not occur and shivering was not interrupted.

Although in the unanaesthetized cat intraperitoneal tranylcypromine had little effect on temperature, it produced a rise on intraventricular injection. Injected in a dose of 0·1 mg the rise was the sole effect, but with a

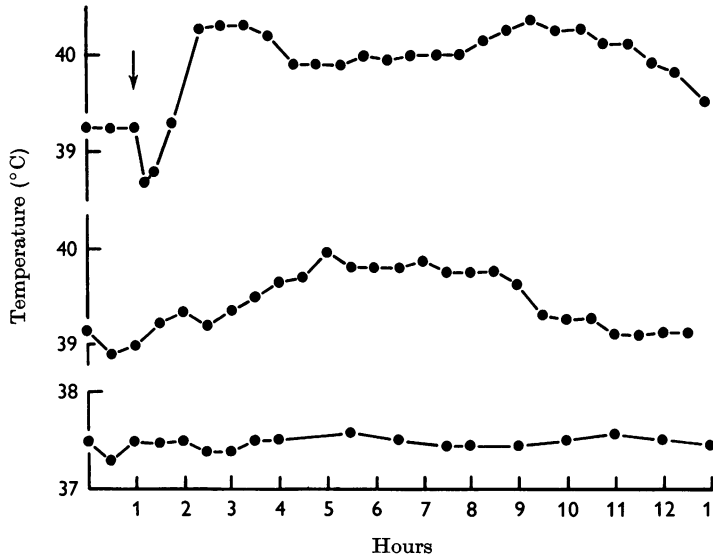

Fig. 7. Records of rectal temperature from an unanaesthetized cat. The three temperature curves were obtained at intervals of at least 4 days. At the arrow, injection of tranylcypromine. Upper curve, 0·5 mg intraventricularly; middle curve, 0·1 mg intraventricularly; lower curve, 0·5 mg intraperitoneally.

larger dose (0·5 mg) the rise was preceded by a fall which lasted for 30–90 min. A typical experiment is illustrated in Fig. 7. The middle curve shows the long-lasting rise in temperature produced by 0·1 mg. The rise was associated with shivering. The upper curve was obtained on the same cat with 0·5 mg. With this dose the rise in temperature was preceded by a fall which lasted about $\frac{1}{2}$ hr and coincided with warming of the ears and cessation of shivering. The lower curve shows that an intraperitoneal injection of 0·5 mg tranylcypromine did not affect rectal temperature.

Cats anaesthetized with pentobarbitone sodium also responded with a rise in temperature to intraventricular injections of tranylcypromine, as illustrated in Fig. 8. The two temperature curves were obtained at an interval of 5 weeks from a cat which had an indwelling cannula in the left

lateral ventricle. The upper curve shows the effect of 0·5 mg tranylcypromine injected twice intraventricularly during the fall in temperature produced by pentobarbitone sodium. After the first injection the fall was halted for about 1 hr. During this time the cat shivered and the ear vessels were contracted. As temperature began to fall again, shivering stopped but the ear vessels remained contracted. The second injection produced a steep rise in temperature with vigorous shivering. Temperature then stayed high for several hours whilst shivering continued and the ear vessels re-

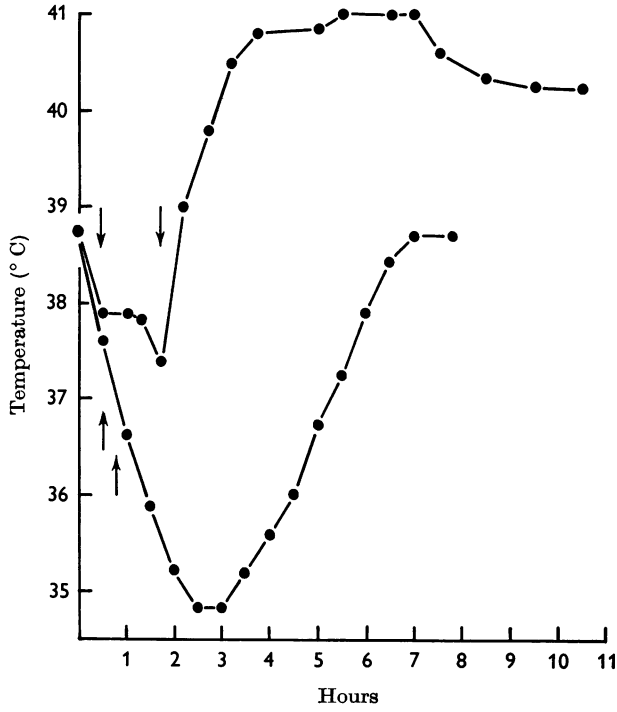

Fig. 8. Records of rectal temperature from a cat anaesthetized with intraperitoneal pentobarbitone sodium (30 mg/kg). The two temperature curves were obtained at an interval of 5 weeks and begin about 10 min after the injection of pentobarbitone sodium. At the upper arrows (↓) intraventricular injection, at the lower arrows (↑) intraperitoneal injection, of tranylcypromine (0·5 mg).

mained contracted. The lower curve serves as control. It shows that the fall in temperature following the pentobarbitone sodium injection was not interrupted when the 0·5 mg tranylcypromine was injected twice intraperitoneally.

In experiments in which 1 mg tranylcypromine was injected intraventricularly, one injection was sufficient to produce a steep rise in tem-

perature which was sustained for many hours and associated with vigorous shivering and constriction of the ear vessels.

Other effects observed with the intraventricular injections of 0·5 or 1 mg tranyclypromine into cats anaesthetized with pentobarbitone sodium were a rise in arterial blood pressure, an increase in heart rate, and respiratory changes. The depth of respiration increased and deep sigh-like breaths occurred from time to time; the rate decreased during the time the blood pressure was at its highest, but subsequently it increased. These effects are illustrated in Fig. 9.

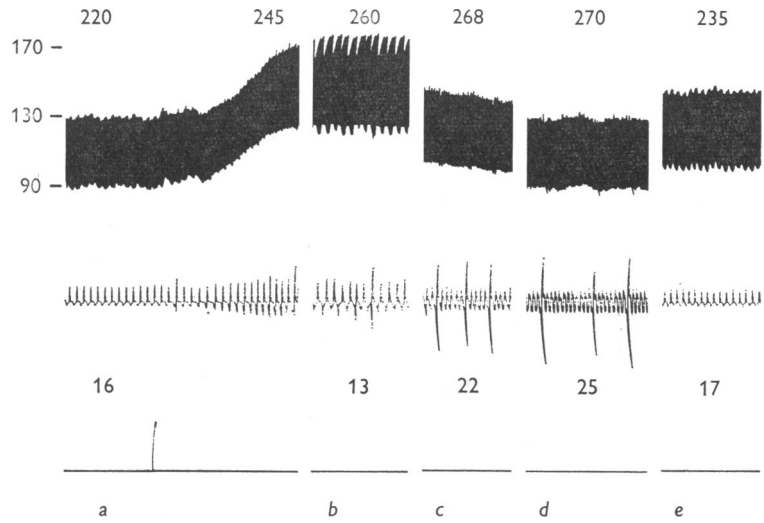

Fig. 9. Arterial blood pressure (upper record) and respiration (lower record) of a cat anaesthetized with intraperitoneal pentobarbitone sodium (33 mg/kg). In record *a*, at the signal, intraventricular injection of tranylcypromine (1 mg). Records *b*, *c*, *d* and *e*, taken 3, 6, 20 and 90 min after the injection. Calibration of blood pressure in mm Hg. The figures on top of the tracing refer to heart rate, those below to respiratory rate/min.

Experiments on rabbits

Pentobarbitone sodium. On slow infusion of pentobarbitone sodium (25 mg/kg) into the ear vein, surgical anaesthesia was obtained. Shivering occurred when about half this amount had been infused. At this stage the rabbit, lightly anaesthetized, was lying on its side, but the corneal reflex was still present. Shivering was observed as fine tremor of the ears and was sometimes seen also in other muscles of the face and in the neck. Usually, shivering stopped before the full dose was infused. The state of surgical anaesthesia was not maintained for long, and in order to prevent the rabbit from coming out of the anaesthesia, the infusions had to be repeated at intervals varying between 60 and 150 min.

The effect on rectal temperature of the intravenous infusions of pentobarbitone sodium was only slight when examined under the same conditions under which the pentobarbitone sodium anaesthesia in cats produced a long-lasting deep fall in temperature, i.e. when no external heat was applied but excessive dissipation of heat was prevented by placing the animal on a cotton-wool pad. Under this condition, rectal temperature fell 0·2° C or less on the infusion of pentobarbitone sodium and the fall was followed by a gradual rise beyond the pre-infusion level as anaesthesia lightened, or a gradual rise occurred without the initial fall. With the repeated infusions of pentobarbitone sodium, there was a tendency for rectal temperature to rise. A typical experiment showing the effects of three

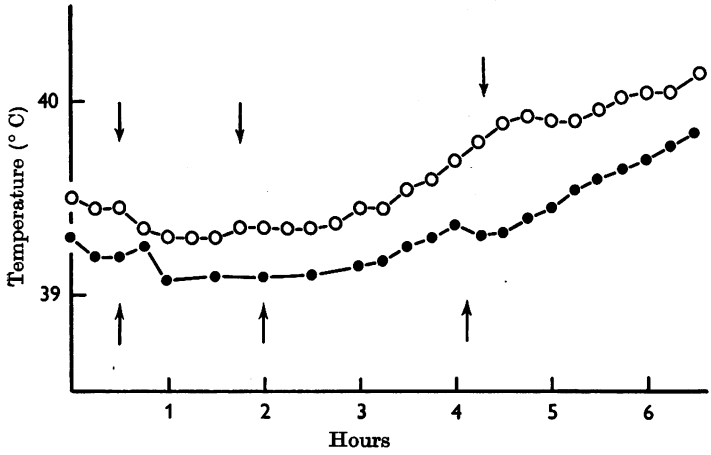

Fig. 10. Records of rectal temperature from one rabbit. The two temperature curves were obtained at an interval of 6 days. At the arrows, intravenous infusions of pentobarbitone sodium (25 mg/kg). ●——●, effect of the pentobarbitone sodium injections alone. O——O, effect of the pentobarbitone sodium injections after an intraperitoneal injection of tranylcypromine (10 mg/kg) given at the beginning of the record.

infusions of pentobarbitone sodium is illustrated by the lower curve of Fig. 10.

On the other hand, when the rabbit was placed on a metal operating table which allows for excessive heat dissipation by conduction, rectal temperature fell steeply after the intravenous infusion of pentobarbitone sodium. When the animal was subsequently insulated from the table by placing it on a cotton-wool pad the fall was halted or, as shown in Fig. 11, reversed.

Tranylcypromine. Unanaesthetized rabbits were observed up to 45 min following an intraperitoneal injection of tranylcypromine (10 mg/kg). No definite changes in rectal temperature or any other effects were observed.

Tranylcypromine (1 mg) also had no effect on rectal temperature when injected through an indwelling cannula into the lateral ventricle of an unanaesthetized rabbit, as shown in Fig. 12. This figure also gives, for comparison, the effect of an intraventricular injection of 25 μg noradrenaline, which produced a rise in rectal temperature of 1·6 °C; in contrast the hypothermic effect of two subsequent intraventricular injections of 200 μg 5-HT was slight, and even doubtful.

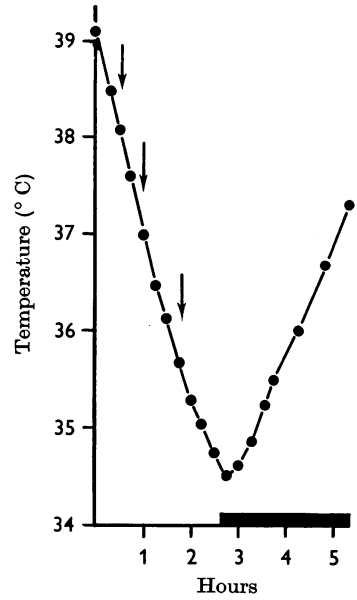

Fig. 11. Record of rectal temperature from a rabbit anaesthetized by an intravenous infusion of pentobarbitone sodium (25 mg/kg) and placed on a metal operating table. The temperature curve begins at the onset of anaesthesia. Intraventricular injections of tranylcypromine (1 mg) at the first arrow, and of noradrenaline (25 μg) at the second and third arrows. During the second half of the experiment the rabbit was lying on a cotton-wool pad, indicated by the horizontal black bar.

Anaesthesia did not reveal an effect by tranylcypromine on rectal temperature, as it did in cats. The upper curve of Fig. 10 begins immediately after an intraperitoneal injection of tranylcypromine (10 mg/kg) and shows the effects of three subsequent intravenous infusions of pentobarbitone sodium. The curve follows the same pattern as that of the lower curve which was obtained 6 days earlier and shows the effect of three such infusions alone. Tranylcypromine (10 mg/kg) had also no effect when injected intraperitoneally into an anaesthetized rabbit lying on a metal operating table whilst temperature was falling steeply.

The effect of tranylcypromine (1 mg) injected into the cerebral ventricles of anaesthetized rabbits was investigated under both conditions with the

rabbit lying on a cotton-wool pad or on a metal operating table. In neither condition did the intraventricular injection of tranylcypromine affect rectal temperature. Noradrenaline (25 μg) similarly injected raised rectal temperature, but only when the rabbit was lying on a cotton-wool pad. When it was lying on the metal operating table, noradrenaline also was ineffective, and temperature continued to fall, as is illustrated in Fig. 11.

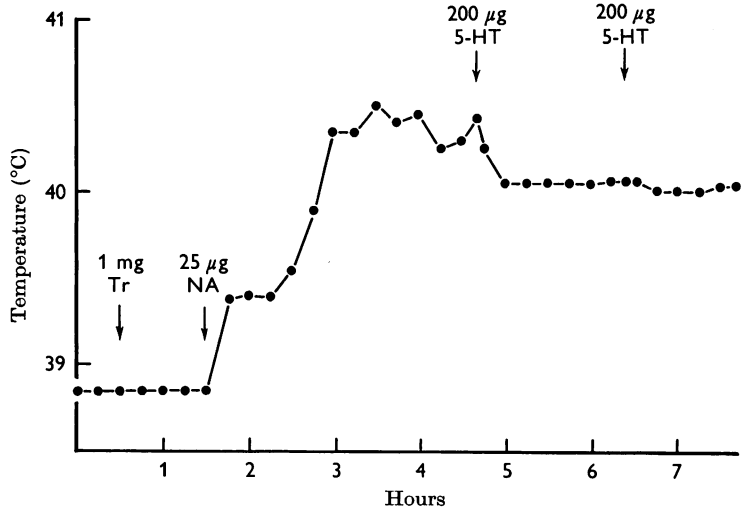

Fig. 12. Record of rectal temperature from an unanaesthetized rabbit. Same rabbit as Fig. 11. Intraventricular injection of tranylcypromine (1 mg) at the first, of noradrenaline (25 μg) at the second, and of 5–HT (200 μg) at the third and fourth arrows.

DISCUSSION

The finding that intraperitoneal injections of tranylcypromine have only a slight temperature-elevating effect in unanaesthetized cats, but that they prevent the profound fall in body temperature produced by anaesthetics such as pentobarbitone sodium or chloralose, and further that they have no effect on body temperature in rabbits, anaesthetized or unanaesthetized, can be readily explained by inhibition of the monoamine oxidase in the hypothalamus brought about by the tranylcypromine.

In cats, the brain level of 5-HT increases, whereas that of adrenaline or noradrenaline remains unchanged after inhibition of monoamine oxidase by its inhibitors. This suggests that 5-HT is, but noradrenaline or adrenaline is not, a substrate for this enzyme in the cat's brain. Since 5-HT raises and the catecholamines lower body temperature when acting on the hypothalamus of the cat, only a rise and not a fall of temperature could be expected when the destruction of 5-HT released in the hypothalamus is prevented by inhibition of monoamine oxidase.

The fact that in unanaesthetized cats intraperitoneal tranylcypromine is effective in large doses only, and that even with these the rise in temperature is relatively small, suggests that the degree of inhibition of monoamine oxidase produced by tranylcypromine given by the intraperitoneal route is not sufficient to affect body temperature greatly. The condition is different in anaesthesia. It has been suggested (Feldberg & Myers, 1964*b*) that anaesthetics increase the release of the three monoamines, 5-HT, adrenaline and noradrenaline, in the hypothalamus, but that the hypothermic action of the released catecholamines predominates—therefore the fall in temperature in anaesthesia. However, the degree of inhibition of monoamine oxidase produced by intraperitoneal injection of even small doses of tranylcypromine would appear to be sufficient to delay the destruction of the increased amounts of 5-HT released during anaesthesia. Consequently, the hyperthermic effect of the 5-HT is able to counteract the hypothermic effect of the released catecholamines, with the result that temperature no longer falls but may even rise.

The ability of tranylcypromine to prevent the fall in body temperature produced in cats by anaesthetics without lightening the anaesthesia strongly supports the idea that the fall in temperature is not simply the result of an 'anaesthetizing' or paralysing effect of the anaesthetics on the hypothalamus, although such an action is not excluded when anaesthesia becomes dangerously deep.

The foregoing interpretation of the hyperthermic effect of intraperitoneal tranylcypromine in cats is based on the assumption that tranylcypromine acts centrally. This view is supported by the finding that injections into the cerebral ventricles produce rises of temperature in doses very much smaller than those effective on intraperitoneal injection. However, the question arises whether the great rises produced by intraventricular tranylcypromine are due solely to inhibition of monoamine oxidase in the hypothalamus or whether they are partly at least the result of a direct 5-HT-like effect on the hypothalamus corresponding to the contractions tranylcypromine produces on smooth muscle preparations such as the cat's nictitating membrane (Tsai & Fleming, 1965) or the fundus strip of the rat's stomach (El Hawary *et al.* 1966). On the fundus strip, strong concentrations produce contraction followed by relaxation. A biphasic effect was obtained also on temperature when tranylcypromine was injected intraventricularly in larger doses, the rise in temperature being preceded by a fall. This fall may signify a central paralysing effect of the tranylcypromine but it could also be explained differently. Carlsson, Lindqvist & Magnusson (1960) discuss the possibility that monoamine oxidase inhibitors not only inhibit the enzyme but also release noradrenaline in the brain and that this effect precedes the enzyme inhibition. The initial fall in temperature

on intraventricular injection of the larger doses of tranylcypromine could thus be due to the release of noradrenaline in the hypothalamus.

On the assumption that anaesthetics increase the release of the monoamines in the hypothalamus, anaesthesia should affect body temperature in rabbits differently than in cats, because the catecholamines cause a rise in body temperature when acting on the hypothalamus of the rabbit, and 5-HT causes a fall which, however, is small and is not obtained consistently. Thus the monoamines not only act differently in rabbits than in cats, but the hypothalamus of the rabbit apparently lacks an efficient hypothermic monoamine. This would explain why body temperature does not fall when the rabbit is anaesthetized with intravenous pentobarbitone sodium under conditions in which this anaesthesia produces a profound fall of temperature in the cat. In fact, if the anaesthetics were to increase the release of monoamines in the rabbit one would expect temperature to rise. Although there was a tendency for the temperature to rise in pentobarbitone sodium anaesthesia, the effect was small. It may therefore be that the anaesthetics do not greatly increase the release of the monoamines in the hypothalamus of rabbits. This would also explain why intraperitoneal tranylcypromine did not affect body temperature, not only in the unanaesthetized but also in the anaesthetized rabbit. It would, however, not explain why tranylcypromine is also ineffective on injection into the cerebral ventricles. No rise would be expected either from a direct 5-HT-like effect, or from persistence of undestroyed 5-HT, because the hypothalamus of the rabbit is rather insensitive to 5-HT and responds to it with a fall in temperature. However, the substrate for the monoamine oxidase in the rabbit's brain is not only 5-HT but adrenaline and noradrenaline as well, and inhibition of their destruction in the hypothalamus should result in a rise of temperature. It is possible that to obtain a rise in tenperature similar to that produced in cats on inhibition of monoamine oxidase, it would be necessary to inhibit the other enzyme for the destruction of the catecholamines as well, i.e. the *o*-methyl-transferase.

Although body temperature was scarcely affected in rabbits during pentobarbitone sodium anaesthesia as long as excessive dissipation of heat was prevented by placing the rabbit on a cotton-wool pad, a steep fall occurred when the anaesthetized rabbit was lying on a metal operating table. This shows that in rabbits, too, temperature regulation is disturbed during anaesthesia. In this condition the catecholamines no longer produced a rise in body temperature when injected into the cerebral ventricles, and this inability of the catecholamines to raise body temperature when acting on the hypothalamus may be one of the factors responsible for the fall in temperature.

We do not know how the monoamines act on the hypothalamus of man,

but it is likely that they act similarly to the way they act in cats, because the hypothalamus of the monkey responds to the monoamines as in cats (W. Feldberg, R. F. Hellon & V. J. Lotti, unpublished experiments). Intraperitoneal tranylcypromine may therefore also prevent the fall in temperature produced in anaesthesia in man, and the question arises as to whether it would have such an action in other conditions of hypothermia as well. It is well known that certain cases of brain injury are associated with profound disturbances in temperature regulation. In some, high fever occurs which has been attributed to an abnormal release of 5-HT in the hypothalamus (Feldberg & Myers, 1966); others are associated with deep hypothermia. It would be worth while to find out if this condition could be alleviated by injections of tranylcypromine.

REFERENCES

Carlsson, A., Lindqvist, M. & Magnusson, T. (1960). On the biochemistry and possible functions of dopamine and noradrenaline in brain. In *Adrenergic Mechanisms*, ed. Vane, J. R., Wolstenholme, G. E. W. & O'Connor, Maeve, pp. 432–445. London: Churchill.

Carmichael, E. A., Feldberg, W. & Fleischhauer, K. (1964). Methods for perfusing different parts of the cat's cerebral ventricles with drugs. *J. Physiol.* **173**, 354–367.

Cooper, K. E., Cranston, W. I. & Honour, A. J. (1965). Effects of intraventricular and intrahypothalamic injection of noradrenaline and 5-HT on body temperature in conscious rabbits. *J. Physiol.* **181**, 852–864.

El Hawary, M. B. E., Feldberg, W. & Lotti, V. J. (1966). Monoamine oxidase inhibition: effect on 5-hydroxytryptamine output from perfused third ventricle and body temperature. *J. Physiol.* **188**, 131–140.

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

Feldberg, W. & Myers, R. D. (1964*b*). Temperature changes produced by amines injected into the cerebral ventricles during anaesthesia. *J. Physiol.* **175**, 464–478.

Feldberg, W. & Myers, R. D. (1965). Changes in temperature produced by micro-injections of amines into the anterior hypothalamus of cats. *J. Physiol.* **177**, 239–245.

Feldberg, W. & Myers, R. D. (1966). Appearance of 5-hydroxytryptamine and an unidentified pharmacologically active lipid acid in effluent from perfused cerebral ventricles. *J. Physiol.* **184**, 837–855.

Feldberg, W. & Sherwood, S. L. (1953). A permanent cannula for intraventricular injections in cats. *J. Physiol.* **120**, 3*P*.

Pscheidt, G. R., Morpurgo, C. & Himwich, H. E. (1962). Norepinephrine and 5-hydroxytryptamine in various species. Regional distribution in the brain, response to monoamine oxidase inhibitors, comparison of chemical and biological assay methods for norepinephrine. *Comparative Neurochemistry*, ed. Richter, D., pp. 401–412. Oxford: Pergamon Press, 1964.

Spector, S. (1963). Monoamine oxidase in control of brain serotonin and norepinephrine content. *Ann. N.Y. Acad. Sci.* **107**, 856–861.

Spector, S., Shore, P. A. & Brodie, B. B. (1960). Biochemical and pharmacological effects of the monoamine oxidase inhibitors iproniazid, 1-phenyl-2-hydrazinopropane (JB 516) and 1-phenyl-3-hydrazinobutane (JB 835). *J. Pharmac. exp. Ther.* **128**, 15–21.

Tsai, T. H. & Fleming, W. W. (1965). Sympathomimetic action of monoamine oxidase inhibitors in the isolated nictitating membrane of the cat. *Biochem. Pharmac.* **14**, 369–371.

Vane, J. R. (1957). A sensitive method for the assay of 5-hydroxytryptamine. *Br. J. Pharmac. Chemother.* **12**, 344–349.

Vogt, M. (1959). Catecholamines in brain. *Pharmac. Rev.* **11**, 483–489.