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Effects of monoamine oxidase inhibitors on the hypothermia produced in cats by halothane

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1. In cats, the effects of intraperitoneal injections of four monoamine oxidase (MAO) inhibitors, tranylcypromine, pheniprazine, pargyline, and nialamide, were examined on rectal temperature and on the hypothermia during anaesthesia produced by a 2 hr period of halothane inhalation.

2. A 2 hr period of halothane inhalation produced a steady fall in temperature amounting to between 2° and 3·5° C. After discontinuation of halothane inhalation, temperature quickly returned to the pre-anaesthetic level but no pyrexia developed. A peculiar stiffness of the leg muscles occurred in several experiments either at the beginning of the inhalation or after its discontinuation.

3. An injection of tranylcypromine (5 mg/kg) caused a rise in rectal temperature and prevented the hypothermia of halothane anaesthesia. This effect lasted for at least 4 hr ; 20 hr after the injection, halothane again caused hypothermia.

4. An injection of pheniprazine (10 mg/kg) usually caused a small rise in temperature which was not sustained. Pheniprazine not only prevented the hypothermia of halothane anaesthesia during the subsequent 20 hr, but during the first few hours after the injection halothane inhalation actually produced a steep rise in temperature.

5. An injection of pargyline (50 mg/kg) had no effect on temperature but the hypothermia due to halothane inhalation was prevented 1 hr after the injection and attenuated after 20 hr. Injection of 200 mg/kg caused a steady rise in temperature which was accelerated when halothane was administered 1 hr later.

6. An injection of nialamide (10, 25 or 50 mg/kg) had no immediate effect on temperature, but pyrexia developed overnight after the two larger doses. The effect on the hypothermia due to halothane inhalation was greater 20 hr after the injection than it was after 1 to 2 hr. Twenty hours after injection of the two larger doses, halothane no longer produced hypothermia but caused a lethal rise in temperature either during or after its inhalation.

7. In rabbits, the effect on temperature of halothane inhalation varied. Either temperature rose slightly or it fell, but not as much as in cats. In one rabbit in which the inhalation had produced a transient rise, pyrexia developed 40 min after discontinuation of halothane.

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The present experiments are concerned with the effect of four inhibitors of monoamine oxidase (MAO) on the hypothermia produced in cats by a volatile anaesthetic.

It has been suggested (Feldberg & Myers, 1964b) that anaesthetics affect body temperature by releasing the monoamines in the anterior hypothalamus. In cats in which noradrenaline lowers and 5-hydroxytryptamine (5-HT) raises body temperature, when acting on the anterior hypothalamus (Feldberg & Myers, 1964a), anaesthetics produce a fall in body temperature, but pre-treatment with the MAO inhibitor tranylcypromine prevents this fall (Feldberg & Lotti, 1967).

Hypothermia of anaesthesia was explained by release of noradrenaline; release of 5-HT was not excluded but the action of noradrenaline was thought to predominate. The effect of tranylcypromine was explained by the finding that, in cats, only 5-HT appears to be a substrate for the brain MAO, since in cats treated with MAO inhibitors, the 5-HT, but not the noradrenaline, level rises in the brain (Vogt, 1959; Brodie, Spector & Shore, 1959; Funderburk, Finger, Drakontides & Schneider, 1962; Spector, 1963). Therefore, after MAO inhibition the released 5-HT is no longer destroyed and overcomes the hypothermic effect of the released noradrenaline. Another explanation is based on the recent finding (Feldberg, unpublished) that pretreatment with tranylcypromine prevents the temperature lowering effect of noradrenaline injected into the cerebral ventricles of the cat. Tranylcypromine may therefore prevent the fall in temperature by rendering the anterior hypothalamus insensitive to the action of the released noradrenaline.

Hitherto, the prevention of the hypothermic effect of anaesthesia by MAO inhibition has been obtained only with tranylcypromine. Since this inhibitor has strong amphetamine-like actions (Goldberg & Sjoerdsma, 1959; Kinross-Wright, 1959; Spencer, 1960; Lee, Shin & Shideman, 1961) its effect might not have been due wholly, or even in part, to inhibition of brain MAO. This possibility would be excluded if it could be shown that the hypothermia is prevented not only by tranylcypromine or pheniprazine, both of which have amphetamine-like actions (Goldberg & Sjoerdsma, 1959; Kinross-Wright, 1959), but also by nialamide and pargyline, two MAO inhibitors without these actions (Goldberg, 1964). Further, the effect of tranylcypromine has so far been observed only on the hypothermia produced by two non-volatile anaesthetics, pentobarbitone sodium and chloralose. In the present experiments, therefore, halothane was used to produce anaesthesia and the effects of tranylcypromine, pheniprazine, nialamide and pargyline were examined on the hypothermia produced by this volatile anaesthetic.

This paper also deals with the effect of halothane on body temperature in the rabbit. The hypothalamus of the rabbit apparently lacks a monoamine which efficiently lowers body temperature, because in this species noradrenaline raises body temperature whereas 5-HT has a weak and irregular hypothermic effect when injected into the cerebral ventricles or directly into the anterior hypothalamus (Cooper, Cranston & Honour, 1965). The theory that the temperature effects of anaesthetics result from release of monoamines in the hypothalamus would find support if, in rabbits, the anaesthetics were to produce a weak and irregular fall or a rise in temperature. So far, this problem has been investigated only with barbiturates. With intravenous injection of pentobarbitone sodium, surgical anaesthesia could be produced without a fall in temperature (Ruckebusch, Grivel & Laplace, 1965; Feldberg & Lotti, 1967) and Ruckebusch *et al.* found that thiopentone sodium, which lowered temperature in cats, raised it in rabbits.

Methods

The experiments were done on cats and Himalayan rabbits of either sex. The cats weighed between 2·1 and 3·3 kg, the rabbits between 2·2 and 2·5 kg. Rectal temperature was measured at room temperature (20°–22·5° C) 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. 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.

Before a cat was anaesthetized, it was kept in a cage: for anaesthesia it was taken out, placed on an operating table, and laid on its left side. The floor of the cage and the surface of the operating table were each covered with a cotton wool pad enclosed in a polythene sheath.

Before a rabbit was anaesthetized it was placed in a Perspex restrainer which consisted of a rectangular base, two vertical sides and a front piece joining the sides. The front piece was inclined at an angle of 50° to the base, and had a U-shaped opening at the top which could be closed with another piece of Perspex to leave a circular hole just large enough to take the neck of the rabbit. The rabbit was placed in the restrainer with its head protruding through the U-shaped opening, the top of which was then closed. For anaesthesia, the rabbit was removed from the restrainer and placed on its left side on the cotton wool pad covering the operating table.

For the halothane (Fluothane I.C.I. Ltd) anaesthesia, the semi-closed system was used. A cone-shaped rubber mask to which a Ruben valve (Ruben, 1955) was attached, was placed over the muzzle of the animal. The valve was connected to a Fluotec vaporiser (Cyprane Ltd, Keighley, Yorks). The gas passing through the vaporiser at a rate of 3 l./min consisted of 80% nitrous oxide and 20% oxygen (v/v). A thermistor probe was placed about 10 cm from the Ruben valve in the gas stream to measure its temperature. It varied between 20·5° and 22° C. For induction, the dial of the vaporiser was set at 3% and for maintenance of anaesthesia at 1% halothane. When the animals were unconscious the face mask was fixed in position with strings.

MAO inhibitors used. Tranylcypromine sulphate (Parnate) kindly supplied by Dr. P. Hey, Smith, Kline & French ; pheniprazine hydrochloride by Dr. R. C. Ursillo, Lakeside Laboratories, Milwaukee, U.S.A., pargyline hydrochloride by Abbott Laboratories, and nialamide by Dr. H. Reinert, Pfizer Ltd, Sandwich, Kent. The drugs were dissolved in sterile pyrogen-free 0·9% NaCl solution and injected intraperitoneally with sterile syringes and needles. Nialamide had to be acidified by a few drops of N HCl to become soluble. The doses refer to the salts.

Results

Experiments on cats

In cats, anaesthesia produced by inhalation of halothane was associated with hypothermia. Rectal temperature began to fall within a few minutes and then continued to fall steadily. During a 2 hr period of inhalation the fall varied between 2° and 3·5° C. Typical effects are shown in records 1 and 4 of Fig. 1, and in records 1 and 5 of Fig. 2. Vasodilatation in the pinnae usually occurred and the skeletal muscles were relaxed, except during the first few minutes of the inhalation, when there was increased muscle tone, and in one experiment, stiffness of the leg muscles.

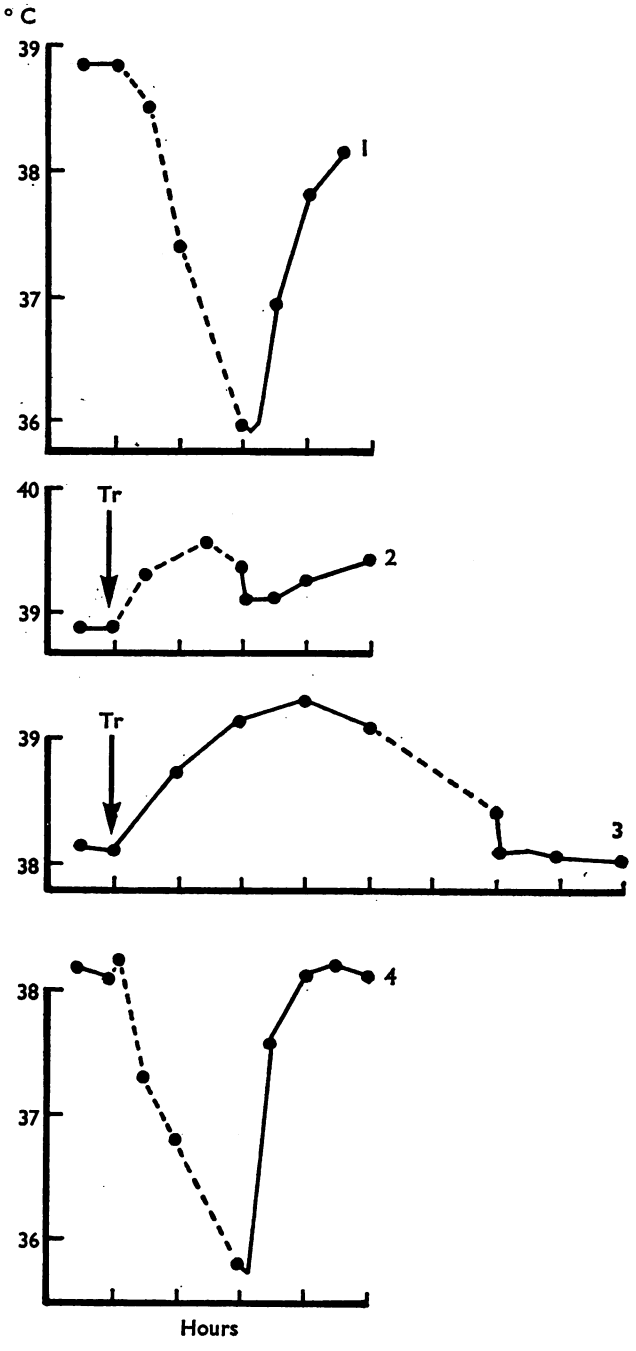

FIG. 1. Records of rectal temperature from one cat. Record 2 obtained 9 days, record 3, 30 days, and record 4, 31 days after record 1. Interrupted lines indicate 2 hr periods of halothane inhalation and arrows marked Tr, intraperitoneal injections of tranylcypromine (5 mg/kg) 2 min after (record 2) and 4 hr before (record 3) the beginning of inhalation.

After discontinuing the halothane inhalation, temperature continued to fall for a few minutes, in some cases even more steeply than during anaesthesia. It then rose steeply and returned to about the pre-injection level within an hour, but no pyrexia was observed. The rise was associated with vigorous widespread shivering, increased muscle tone and vasoconstriction in the pinnae. The cats woke up quickly, but appeared to be confused for several minutes afterwards. They were ataxic for 15–20 min. A peculiar feature seen several times during the first few minutes after discontinuing halothane inhalation was stiffness of the leg muscles. They were strongly contracted and felt hard. The hind legs were extended and the forelegs flexed ; the joints seemed to be locked, since it was difficult to flex the hind or to extend the forelegs.

Tranylcypromine

An intraperitoneal injection of tranylcypromine (5 mg/kg) produced licking movements, profuse salivation and tachypnoea. The pinnae became cold, the eyes opened wide and the pupils dilated. Previously friendly cats became apprehensive ; they objected to being touched and cowered away from a proffered hand. Retching and vomiting occurred in most experiments. Rectal temperature rose by between 0·5 and 1·2° C and in one experiment by as much as 1·9° C. Similar responses were obtained to intraperitoneal injections of 10 mg/kg tranylcypromine by Feldberg & Lotti (1967).

The fall in temperature during a 2 hr period of halothane anaesthesia did not occur when tranylcypromine (5 mg/kg) was injected intraperitoneally 2 min after the onset of inhalation. Instead, temperature rose as if tranylcypromine had been given alone. Nevertheless, the cat became fully anaesthetized. Figure 1 shows that the fall of 2·9° C during a 2 hr period of halothane anaesthesia (record 1) was replaced by a rise of 0·7° C when on another day tranylcypromine was injected at the beginning of the anaesthesia (record 2). The rise occurred during the first hour and a half and was followed by a fall of 0·2° C during the last half-hour of inhalation. The temperature effect of tranylcypromine alone is shown in record 3. The injection produced a rise of 1·2° C during the first 3 hr ; temperature then began to fall and continued to fall at about the same rate when halothane was given 1 hr later. During the 2 hr period of inhalation temperature fell by only 0·7° C. Thus 4 hr after the tranylcypromine injection the normal hypothermic response to halothane had not returned. However, when the halothane inhalation was repeated 25 hr after the injection, the effect of tranylcypromine was no longer evident. As shown in record 4 temperature fell by 2·5° C during the 2 hr period of inhalation.

In the experiments in which tranylcypromine prevented the hypothermic effect of halothane, the ear vessels remained constricted and the skeletal muscles were not fully relaxed. Tranylcypromine given in the first few minutes of halothane anaesthesia produced tachypnoea, but less than in the unanaesthetized cat. When halothane was applied 4 hr after tranylcypromine, while tachypnoea was still present, respiration slowed but became quicker again when the inhalation of halothane was discontinued. The cessation of halothane inhalation was usually followed by a fall in temperature of between 0·2° and 0·4° C during the first few minutes, as shown in records 2 and 3 of Fig. 1. Stiffness of the leg muscles developed in one experiment at the beginning of the anaesthesia and in another after removal of the halothane.

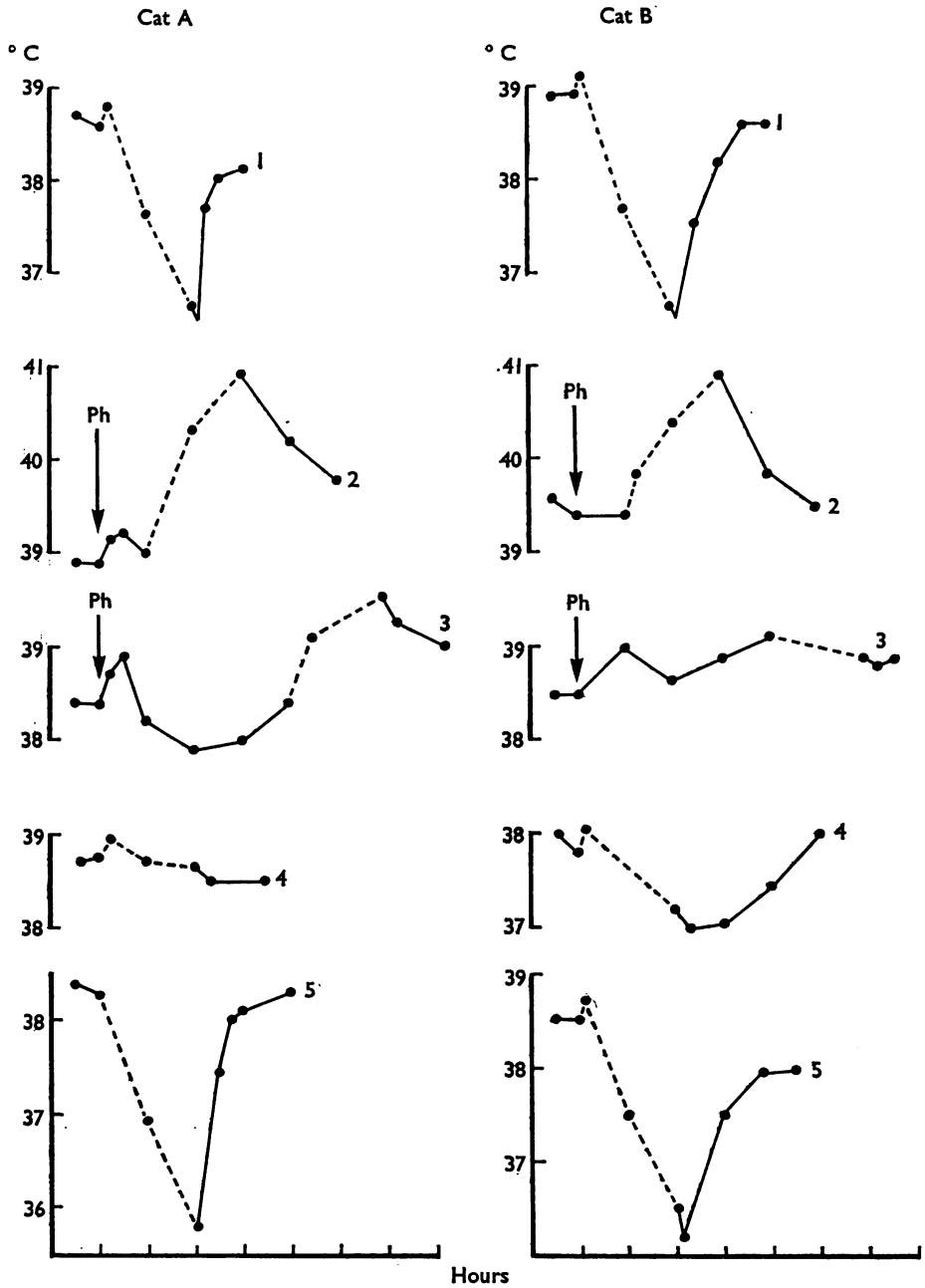

FIG. 2. Records of rectal temperature from two cats. Records 1, 2, 3 and 4 obtained at intervals of between 4 and 16 days, and record 5, 1 day after record 4. Interrupted lines indicate 2 hr periods of halothane inhalation and arrows marked Ph, intraperitoneal injections of pheniprazine (10 mg/kg) 1 hr (records 2) and 4 hr (records 3) before the halothane inhalation. In records 4, beginning of halothane inhalation 20 hr and in records 5, 45 hr after pheniprazine (10 mg/kg).

Pheniprazine

As with tranylcypromine, licking movements, profuse salivation, constriction of the ear vessels, widening of the eyes, mydriasis, tachypnoea and emesis were observed following the intraperitoneal injection of pheniprazine (10 mg/kg). Retching and vomiting occurred 40 to 60 min after the injection, then recurred up to four times during the second hour and, in one cat, once again after another 2 hr. Vomiting was often followed by defaecation. In two cats there was tear secretion and in some there were short periods of panting with opening of the jaws and protrusion of the tongue, which was deep red in colour. With tranylcypromine, panting had not been observed in cats either in the present experiments or in those of Feldberg & Lotti (1967), but according to Feldberg, Hellon & Lotti (1967) it occurred regularly in dogs.

Sometimes the injection of pheniprazine caused no change in temperature, but usually it produced a rise of about half a degree, which lasted for 30 to 60 min and was sometimes followed by a fall. In one experiment temperature rose by 1° C. Temperature effects obtained in two cats are shown in records 2 and 3 of Fig. 2. Each cat received two injections of pheniprazine. After the first injection, temperature was recorded for 1 hr, and after the second injection for 4 hr before halothane was applied. In cat A, the first injection produced a rise of 0·35° C during the first half hour and the second injection a rise of 0·5° C, followed by a fall. In cat B the first injection produced no change in temperature and the second a rise of about 0·6° C interrupted by a fall during the second hour.

Figure 2 also illustrates the effect of halothane applied at different intervals after the pheniprazine injection. In both cats, halothane given alone caused a fall of over 2° C (records 1) but when applied 1 hr after pheniprazine (records 2) temperature rose. It rose by 2° C in cat A and by 1·5° C in cat B. These rises were not a continuation of rises produced by pheniprazine, because in cat A the small hyperthermic response to pheniprazine had come to an end before halothane was given and in cat B pheniprazine had produced no rise at all. When the halothane inhalation was extended beyond the 2 hr period, temperature continued to rise, but at a much slower rate. For instance, in cat A, the effect of halothane inhalation, 1 hr after a pheniprazine injection, was re-examined 6 weeks later but with the period of anaesthesia extended to 4 hr. During the first 2 hr temperature rose by 1·9° C, and during the second 2 hr by only 0·3° C.

Pheniprazine affected the temperature response to halothane inhalation for a longer time than tranylcypromine. Four hours after the pheniprazine injection halothane still produced a rise in cat A and no change in temperature in cat B (records 3). The rise in cat A was, however, smaller than that after an interval of 1 hr. After 20 hr the inhalation produced scarcely any fall in cat A and a fall of only 0·8° C in cat B (records 4), but after 45 hr the hypothermic response to halothane had fully returned in both cats (records 5).

In those experiments in which temperature either rose, remained unchanged or fell slightly on inhalation of halothane, muscle tone, ear vessels and respiration were affected in the same way as in the experiments in which tranylcypromine prevented the hypothermic response to halothane. In several of these experiments with pheniprazine, stiffness of the leg muscles lasting up to a minute was observed, either at the beginning of anaesthesia or after halothane had been discontinued. When

the pheniprazine injection had preceded the halothane inhalation by only 1 hr, vomiting occurred after recovery from anaesthesia.

Pargyline

Results obtained with 50 mg/kg injected intraperitoneally into one, and 200 mg/kg into another, cat are illustrated in Fig. 3. The injection of 50 mg/kg did not affect temperature and there were none of the effects obtained with tranylcypromine or pheniprazine. Yet temperature did not fall but remained unchanged when halothane was given 1 hr after the injection. This is shown in record 1 of Fig. 3, for cat A. The next day the hypothermic response to halothane had not fully returned. Temperature fell by only 1·2° (record 2) as compared with 2·0° C when halothane inhalation was repeated again after another 3 days (record 3).

The injection of 200 mg/kg produced licking movements, dilatation of the pupils, pronounced tachypnoea and vasconstriction of the pinnae. The cat became apprehensive, and when approached or touched, it drew back, hissing, and piloerection occurred on the tail and back. As shown in Fig. 3 for cat B, temperature rose by 0·7° C during the first hour. When halothane inhalation was then given temperature rose more steeply and reached 41·7° C in 2 hr. After discontinuation of halothane the cat vomited, temperature fell to 41° C within half an hour and then rose again. There was panting, tremor of the head, weakness of the hind legs and diarrhoea. The cat died 3·5 hr later.

Nialamide

This inhibitor of monoamine oxidase also prevented the fall in temperature produced by halothane anaesthesia. The effect was greater 20 hr than 1–2 hr after injection of nialamide. Results obtained with intraperitoneal injections of 10, 25 and 50 mg/kg are illustrated in Fig. 4.

During the first hours after the injections, temperature remained unchanged ; after the two larger doses, vomiting occurred, the only early effect obtained, and pyrexia developed overnight. During the pyrexia there was maximal dilatation of the pupils, tachypnoea, vasoconstriction in the pinnae, shivering, tremor of the head and weakness in the hind legs. The hypothermic response to halothane was affected earlier, as shown for cat A in Fig. 4. Record A_1 shows the effect of halothane alone ; a fall in temperature which amounted to 2·4° C during the 2 hr period of inhalation. On the other hand, record A_2 shows that, when halothane was given 1 hr after an injection of 50 mg/kg of nialamide, temperature fell by only 0·6° C during the first hour of inhalation, and then returned to the pre-anaesthesia level during the second hour. After halothane inhalation was stopped, the rise continued and temperature reached 39·5° C in 2 hr. The cat died overnight.

In another cat in which halothane was given 2 hr after an injection of 50 mg/kg of nialamide, the hypothermic response to halothane was again greatly reduced. This cat developed fever overnight and its rectal temperature was 42·5° C the next day. Inhalation of halothane resulted in a steep rise ; within 15 min temperature rose by about 1° C and the cat died.

Cat B was injected with 25 mg/kg of nialamide. The record begins 20 hr later ; temperature had risen to just over 41° C. Halothane no longer produced its hypothermic effect ; it seemed to have no effect at all on temperature, for the initial rise

of 0·2° C seen in the record may have been due to struggling. However, after halothane inhalation was stopped, temperature began to rise sharply; it reached 44·3° C in 1 hr and the cat died.

The effect of an injection of 10 mg/kg of nialamide is shown in cat C. The record again begins 20 hr later. The hypothermia produced by halothane was reduced, because temperature fell by only 1·1° C during the 2 hr period of inhalation.

Experiments on rabbits

The effect on rectal temperature of a 2 hr period of halothane inhalation varied in different rabbits. In two out of six temperature did not fall during anaesthesia. The results are shown in records A and B of Fig. 5. There was in fact a small rise during the first hour of inhalation not associated with struggling. After discontinuation of halothane inhalation, temperature fell by about 0·5° C in one rabbit and rose steeply to 41° C after a delay of about 40 min in the other. In this rabbit, the pyrexia following anaesthesia was not an incidental effect because it occurred again when halothane was given a few days later, and again there was no fall during the 2 hr period of inhalation. In the remaining four rabbits temperature fell steadily during the anaesthesia, but by only 0·9 to 1·4° C and not below 37·7° C. After discontinuation of halothane, temperature either returned to or rose by about 1° C beyond the pre-anaesthetic level. The results obtained on two of these rabbits are shown in records C and D of Fig. 5. The initial rise in record C at the beginning of anaesthesia was probably due to struggling.

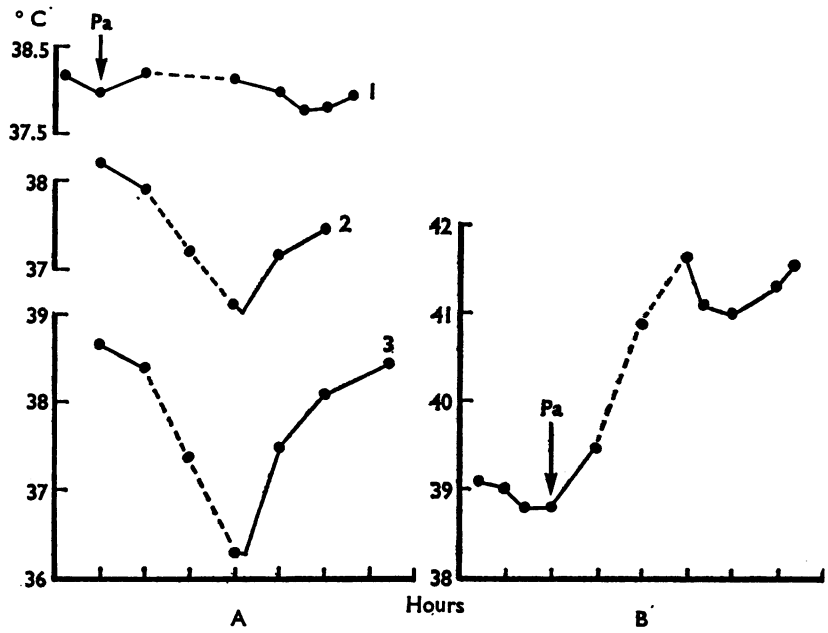

FIG. 3. Records of rectal temperature from two cats. In cat A, record 2 obtained 1 day and record 3 4 days after record 1. Interrupted lines indicate 2 hr periods of halothane inhalation and arrows marked Pa, intraperitoneal injections of pargyline, 50 mg/kg (cat A) and 200 mg/kg (cat B), 1 hr before halothane inhalation.

The rabbits required a longer time (15–20 min) than the cats to wake up after halothane was discontinued, and the peculiar stiffness of the leg muscles, which occurred in some cats either at the beginning or shortly after the end of the halothane inhalation, was not observed.

Discussion

Recently it was shown (Feldberg & Lotti, 1967) that tranylcypromine injected intraperitoneally into cats prevented the hypothermia produced by two non-volatile anaesthetics, pentobarbitone sodium and chloralose. The present experiments show that hypothermia produced by halothane inhalation is also prevented by tranylcypromine and that this action is shared by the three other MAO inhibitors examined, pheniprazine, pargyline and nialamide. As the effect was produced by all four inhibitors the possibility can be excluded that it resulted from amphetamine-like actions, since such actions are produced only by tranylcypromine and pheni-

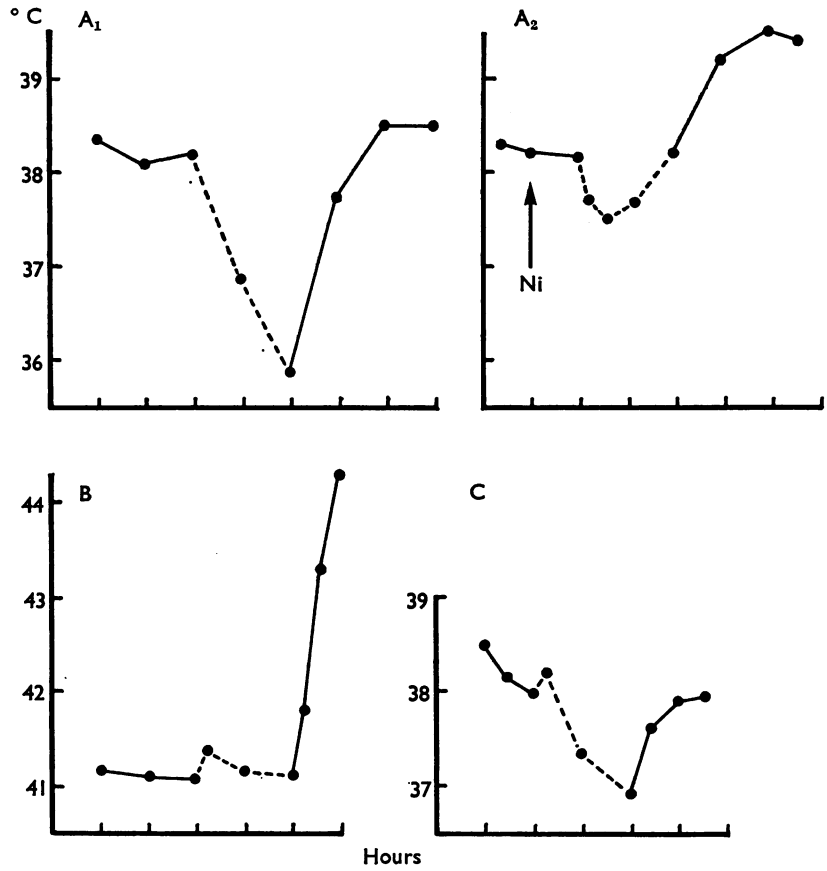

FIG. 4. Records of rectal temperature from three cats. Interval between records 1 and 2 in cat A, 1 month. Interrupted lines indicate 2 hr periods of halothane inhalation. In cat A at the arrow marked Ni, intraperitoneal injection of nialamide (50 mg/kg) 1 hr before halothane inhalation. In cats B and C, beginning of halothane inhalation 20 hr after intraperitoneal injection of nialamide 25 mg/kg (cat B) and 10 mg/kg (cat C).

prazine, not by pargyline and nialamide. The effect is therefore most likely a result of inhibition of MAO, particularly the MAO of the brain. There is good evidence that in cats the brain MAO is inhibited by the four inhibitors when injected in the doses used in the present experiments, because the 5-HT content in the effluent from the perfused cerebral ventricles of anaesthetized cats increases under these conditions. This was first shown by El Hawary, Feldberg & Lotti (1967) for tranylcypromine. Recently Goodrich (1969) found that, weight for weight, tranylcypromine was twice as potent as pheniprazine, eight times as potent as nialamide and sixty times as potent as pargyline in increasing the 5-HT output. Previous experiments (Funderburk *et al.*, 1962 ; Schoepke & Wiegand, 1963), in which the increase in the 5-HT level of the cat brain was studied after repeated subcutaneous or intraperitoneal injections, also show that tranylcypromine and pheniprazine were more potent than nialamide and much more potent than pargyline. This agrees with the relative potencies of these inhibitors in preventing the hypothermia of halothane anaesthesia in the present experiments, although the inhibitors were not tested at several dose levels, a procedure which would have allowed a more accurate comparison.

Tranylcypromine not only prevents the hypothermia produced by anaesthetics but also that produced by the action of noradrenaline in the anterior hypothalamus (Feldberg, unpublished). If it were known that the temperature-lowering effect of noradrenaline was also prevented by the other inhibitors, prevention of the hypothermia of anaesthesia would be satisfactorily explained on this basis. There are three ways in which the hypothermic response to noradrenaline may be prevented, but it is not possible to distinguish between them as long as it is uncertain whether 5-HT and noradrenaline produce their temperature effects by an action on the same or on different cells in the hypothalamus. The hypothalamic cells may be rendered insensitive to noradrenaline by the inhibitors themselves or by the abnormally high

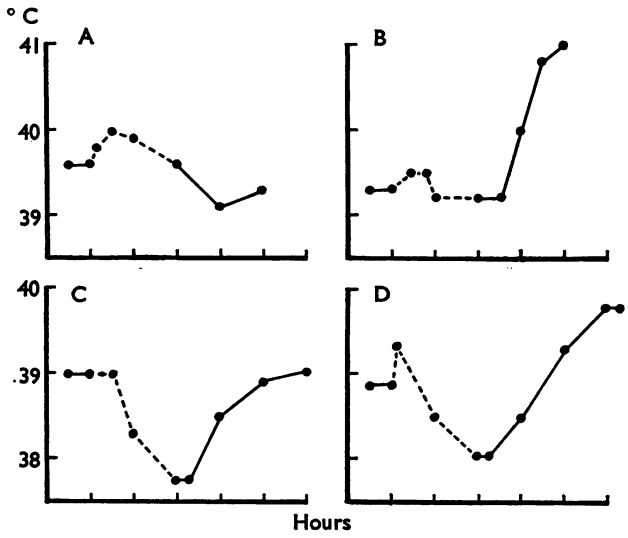

FIG. 5. Records of rectal temperature from four rabbits. Interrupted lines indicate 2 hr periods of halothane inhalation.

5-HT levels resulting from the enzyme inhibition. Alternatively, persistence of undestroyed 5-HT may tend to raise temperature and thus overcome the hypothermic effect of noradrenaline. Another possibility would be that prevention of hypothermia is not solely due to an action of the inhibitors on the hypothalamus but due to an action on structures in the lower brain stem or the spinal cord or even due to a peripheral action.

The inhibitors not only prevented the hypothermia of halothane anaesthesia but also caused rises in temperature. With tranylcypromine, pheniprazine and pargyline, temperature rose in the first hours following their injection ; with nialamide this did not happen but pyrexia developed overnight. Apart from these rises, halothane seemed to be able to provoke or accentuate rises in temperature after the injection of MAO inhibitors. For instance, if given during the first hours following the injection of pheniprazine, halothane inhalation produced a steady rise in temperature even when pheniprazine itself had caused no rise, or when the rise had come to an end before inhalation was begun. With pargyline the rise which followed its injection was accelerated by halothane inhalation and became lethal after the inhalation was stopped ; with nialamide it was found that on the day after injection, during the state of pyrexia which had developed overnight, halothane produced a steep and lethal rise of temperature either during or after the inhalation. It is possible, but not proved, that the rises produced by the inhibitors themselves result from MAO inhibition and accumulation of undestroyed 5-HT in the hypothalamus, whereas the rises provoked by halothane after MAO inhibition result from increased release of 5-HT brought on by the anaesthetic.

The rises provoked by halothane after MAO inhibition are of interest in connection with the rare cases of pyrexia which occur during and after anaesthesia in man. They occur particularly in children and young persons and are often fatal. In most of these unfortunate incidents the anaesthetics used were volatile fluorinated hydrocarbon agents, halothane or methoxyfluorane, but they have also occurred with other anaesthetics (Brown, 1954 ; Saidman, Havard & Eger, 1964 ; Cullen, 1966 ; Davies & Graves, 1966 ; Hogg & Renwick, 1966 ; Lavoie, 1966 ; Relton, Creighton, Johnston, Pelton & Conn, 1966 ; Thut & Davenport, 1966 ; Purkis, Horrelt, de Young, Fleming & Langley, 1967 ; Stephen, 1967 ; Wilson, Dent, Traber, McCoy & Allen, 1967 ; Hawthorne, Richardson & Whitfield, 1968). Recently, lethal pyrexias have also been described in about 17% of pigs anaesthetized with halothane (Harrison, Biebuyck, Terblanche, Dent, Hickman & Saunders, 1968). In none of the present experiments on cats did halothane anaesthesia alone produce pyrexia. Temperature fell during the halothane inhalation and returned to the pre-anaesthetic level after discontinuation of inhalation. On the other hand, in one out of six rabbits pyrexia, though not a lethal one, occurred after discontinuation of the inhalation and the pyrexia was obtained again when the halothane inhalation was repeated. The possibility cannot be excluded that the rare cases of pyrexia produced in man by halothane and by other anaesthetics result from an abnormal release of 5-HT in the hypothalamus, a possibility also envisaged by Horsey (1968), although it is not clear why anaesthetics should provoke an abnormal increase in 5-HT release in these cases. The present finding that pyrexia can develop in cats when halothane anaesthesia is given after injections of MAO inhibitors point to the possible danger of halothane anaesthesia in patients under treatment with MAO inhibitors and suggest special caution when anaesthesia is required in such patients.

The peculiar stiffness of skeletal muscles observed in some cats at the onset or after discontinuation of halothane anaesthesia is probably the same phenomenon as the " severe muscle rigidity " and the " stiffly extended limbs " with " the muscles in extreme spasm " observed in man and pigs during the pyrexia of halothane anaesthesia, but in cats the muscle stiffness was not associated with pyrexia, was transient, and not enhanced by the injections of the MAO inhibitors.

In rabbits a hypothermic response to halothane was not always obtained, and when it occurred the fall was less pronounced than in cats. This difference in the temperature response to an anaesthetic between cats and rabbits is not peculiar to halothane but has been observed with barbiturates as well and has been explained by the assumption that the hypothalamus of rabbits lacks a monoamine which efficiently lowers temperature.

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