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Effects of monoamine oxidase inhibitors and amphetamine on hypothermia produced by halothane

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Summary

1. In cats, the effects of tranylcypromine and pheniprazine, two monoamine oxidase (MAO) inhibitors with strong amphetamine-like actions, of pargyline, an inhibitor without amphetamine-like actions, and of amphetamine itself, were examined on the hypothermia produced by a 2 hr period of halothane inhalation.

2. The hypothermia was prevented by intraperitoneal injections of the three MAO inhibitors. Tranylcypromine and pheniprazine acted in doses of a few milligrams, pargyline in doses of over 100 mg.

3. The hypothermia was prevented by injections into the cerebral ventricles of tranylcypromine and pheniprazine, in doses which were effective also on intraperitoneal injection ; intraperitoneal injections were sometimes more effective. The large doses of pargyline needed to prevent the hypothermia when injected intraperitoneally were not tested by the intraventricular route, as the injections had to be made in a volume of 0·1 ml. In smaller doses intraventricular pargyline was not effective.

4. The hypothermia was prevented by an intraperitoneal or intraventricular injection of amphetamine in a dose as little as 1 mg ; intraperitoneal injections were sometimes more effective.

5. The effects of tranylcypromine and pargyline given intraperitoneally, and of amphetamine given intraventricularly as well, were also examined on the hypothermia produced by an intraventricular injection of 200 μg noradrenaline. The two MAO inhibitors and amphetamine prevented the hypothermia, or greatly reduced it.

6. It is concluded (*a*) that even on intraventricular injection the MAO inhibitors must first be absorbed into the blood stream before they can prevent the hypothermia of a halothane anaesthesia ; (*b*) that their action may not be solely on the anterior hypothalamus ; and (*c*) that they may not act only through MAO inhibition.

Introduction

Monoamine oxidase (MAO) inhibitors, injected intraperitoneally into cats, prevent the hypothermia produced by pentobarbitone sodium, chloralose or halothane

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anaesthesia (Feldberg & Lotti, 1967 ; Summers, 1969). The explanation given for this effect was based on the theory that anaesthetics release the monoamines in the hypothalamus (Feldberg & Myers, 1964). It was assumed that the hypothermia resulted from an action of released noradrenaline which lowers body temperature when acting on this part of the brain and that this action overcame the temperature raising effect of 5-hydroxytryptamine (5-HT) released as well. As first shown by Vogt (1959) in cats, only 5-HT, not noradrenaline, appears to be a substrate of the brain MAO. Its inhibition would therefore prevent the destruction of the released 5-HT, which could then overcome the temperature lowering effect of noradrenaline (Feldberg & Lotti, 1967). The ability of intraperitoneal injections of MAO inhibitors to increase the 5-HT output from the perfused cerebral ventricles in cats (El Hawary, Feldberg & Lotti, 1967 ; Goodrich, 1969) supports this theory.

The present experiments deal with three facets of the action of MAO inhibitors in preventing the hypothermia associated with halothane anaesthesia, and lead to an altered view concerning their mechanism of action. (1) Their action need not solely be on the anterior hypothalamus, because their potency was found not to increase when they were injected into the cerebral ventricles instead of into the peritoneum. (2) Their action need not be due solely to MAO inhibition. Two of the MAO inhibitors which prevented hypothermia have strong amphetamine-like actions and amphetamine itself was found to produce this effect. (3) Their ability to prevent the hypothermia need not be due to the temperature raising effect of undestroyed 5-HT, since it was found that the inhibitors, as well as amphetamine, rendered the anterior hypothalamus insensitive to the temperature lowering effect of intraventricular noradrenaline.

Methods

The experiments were done on cats of either sex, weighing between 2·4 and 3·0 kg. Rectal temperature was measured at room temperature (19°–22·5° C) by a thermistor probe inserted about 10 cm into the rectum and held in position by gently wrapping the protruding end of the probe to the root of the tail with adhesive tape. 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.

For halothane (Fluothane, I.C.I. Ltd.) inhalation the semi-closed system was used and anaesthesia was produced as described by Summers (1969). For intraventricular injection, a Collison cannula was permanently implanted into the left lateral ventricle as described by Banerjee, Feldberg & Lotti (1968).

Drugs used

Tranylcypromine sulphate (Parnate), kindly supplied by Dr. P. Hey, of Smith, Kline & French ; pheniprazine hydrochloride by Dr. R. C. Ursillo, of Lakeside Laboratories, Milwaukee, U.S.A. ; pargyline by Abbott Laboratories ; phenylisopropylamine sulphate (amphetamine), British Drug Houses Ltd. ; noradrenaline acid tartrate (Hoechst A.G., Germany). The doses refer to the salts. The drugs were dissolved in sterile pyrogen-free 0·9% NaCl solution and injected with sterile syringes and needles

Results

MAO inhibitors and amphetamine on hypothermia produced by halothane inhalation

Tranylcypromine

Summers (1969) found that after intraperitoneal tranylcypromine (5 mg/kg), inhalation of halothane no longer lowered but raised body temperature in cats. In the present experiments this effect was obtained with smaller doses and also with injections of tranylcypromine into the cerebral ventricles. The intraperitoneal injections were as effective as those given intraventricularly, if not a little more so. Typical results are shown on three cats in Fig. 1.

In each cat a 2 hr period of halothane inhalation produced a fall in temperature of the order of 2° C, as shown in the top records. In cat A, 2 mg tranylcypromine was given 5 min before and again 30 min after the beginning of the inhalation. Temperature no longer fell, but instead rose about half a degree. This happened whether the injections were made intraperitoneally (record 2) or intraventricularly

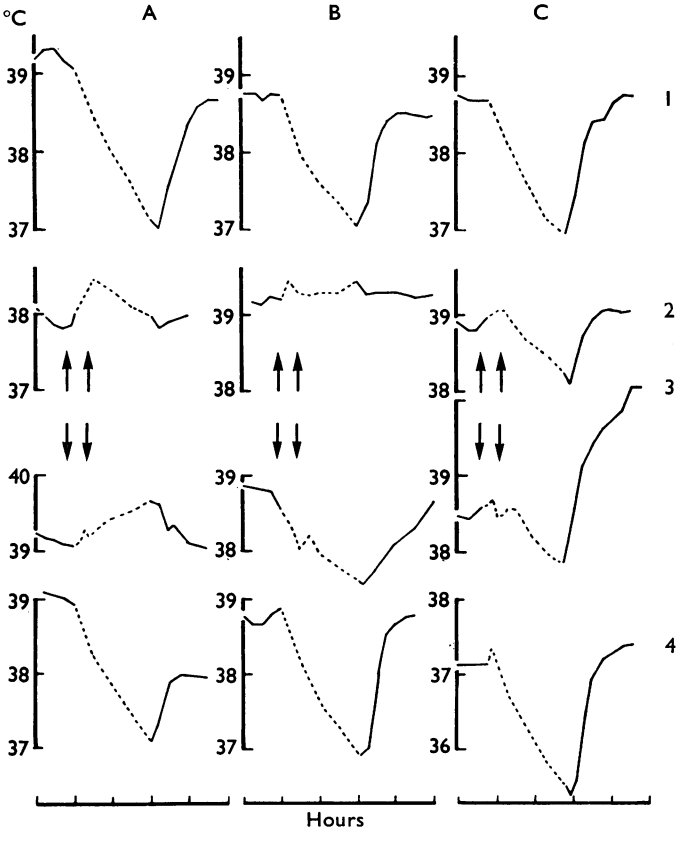

FIG. 1. Records of rectal temperature from three cats (cat A, 2·8 kg; cat B, 2·6 kg; cat C, 2·9 kg). The interrupted lines indicate a 2 hr period of halothane inhalation and the arrows, injections of 2 mg (cat A), 1 mg (cat B), and 0·5 mg (cat C) of tranylcypromine given either intraperitoneally (records 2) or into the cerebral ventricles (records 3). In each cat the four records were obtained on different days. In this and the following figures the directions of the arrows indicate intraperitoneal (↑) and intraventricular (↓) injections.

(record 3). The same procedure of injections was adopted for 1 mg in cat B, and for 0·5 mg in cat C. In cat B, the tranylcypromine converted the halothane hypothermia into a rise of 0·2° C when given intraperitoneally, but only reduced the hypothermia when given intraventricularly. In two similar experiments with 1 mg the same result was obtained in one, in the other the hypothermia was reduced in both conditions, but more by the intraperitoneal injections. In cat C, the halothane hypothermia was reduced to about the same extent whether the preceding injections of 0·5 mg were made intraperitoneally or intraventricularly. In this experiment tranylcypromine injected intraventricularly produced another effect, a large rise in temperature after discontinuation of the halothane inhalation (record 3). The same result was obtained in this cat on another occasion with 1 mg tranylcypromine injected intraventricularly, but it was not encountered in other cats. Twenty-four hours after the tranylcypromine injections, halothane again produced its normal hypothermic effects. This is shown for the three cats in the bottom records (4).

Feldberg & Lotti (1967) describe an experiment in which 0·5 mg tranylcypromine given twice at the beginning of a pentobarbitone sodium anaesthesia was effective in counteracting the hypothermia on intraventricular but not on intraperitoneal injection. When repeating the experiment this result was obtained only once, in several other experiments in which 0·5 mg or 1 mg tranylcypromine was given twice during the first hour of a pentobarbitone sodium anaesthesia, the hypothermia was either not affected, or it was reduced, but there was no difference between intraperitoneal or intraventricular injections. With injections of 2 mg, given twice, the pentobarbitone sodium hypothermia was reduced or abolished, but again tranylcypromine was as effective on intraperitoneal as on intraventricular injection. Thus tranylcypromine given intraperitoneally or intraventricularly affected the hypothermia produced by pentobarbitone sodium in the same way as that produced by halothane.

Pheniprazine

Summers (1969) found that intraperitoneal pheniprazine (10 mg/kg) converted the fall in temperature produced by halothane inhalation into a rise. In the present experiments, pheniprazine was found to affect the halothane hypothermia in much

TABLE 1. *Maximal changes in temperature during a 2 hr halothane inhalation*

		Temperature changes in °C		
			Pheniprazine	
Cat	Dosage of pheniprazine in mg*	Control	Intraventricularly	Intraperitoneally
1	1	−2·0	−2·3	
2	2	−2·1	−2·0	
3	2	−1·7		−1·4
4	2	−1·9		−2·5
5	4	−1·8	−0·8	+0·1
6	4	−2·0	0	−2·0
2	4	−2·1	−0·45	+0·2
7	3×0·5	−2·1	−1·8	
4	3×0·5	−1·1	−0·9	−1·4
5	3×1	−1·8	−1·5	−2·2
8	3×1	−1·4	−1·4	−0·2
9	3×1	−1·4	−1·3	−0·8
5	3×2	−1·8	+1·0	+0·9
2	3×2	−2·1	+0·3	+0·3

* The single doses were injected 1 hr before, the three doses at hourly intervals, the last one again 1 hr before the beginning of the halothane inhalation.

smaller doses and also on intraventricular injection. The efficacy was about the same with both routes of administration. The results are summarized in Table 1.

Single injections of 1 or 2 mg given an hour before the halothane inhalation did not affect the hypothermia. Following the injection of 4 mg the hypothermia was reduced, abolished or converted into a small rise. In two of three cats the fall was converted into a rise by the intraperitoneal, but only reduced by the intraventricular injection ; in the third cat the opposite result was obtained.

With three injections given at hourly intervals, the last injection being given 1 hr before the halothane, no effect was obtained when the dose injected each time was 0·5 mg, but when it was 2 mg the fall was converted into a small rise regardless of the route of administration. The results obtained with 2 mg are illustrated in Fig. 2, which also shows that 24 hr after the last pheniprazine injection halothane again lowered temperature although the hypothermia was not fully restored. Table 1 shows that with the intermediate dose of 1 mg the hypothermia was not affected

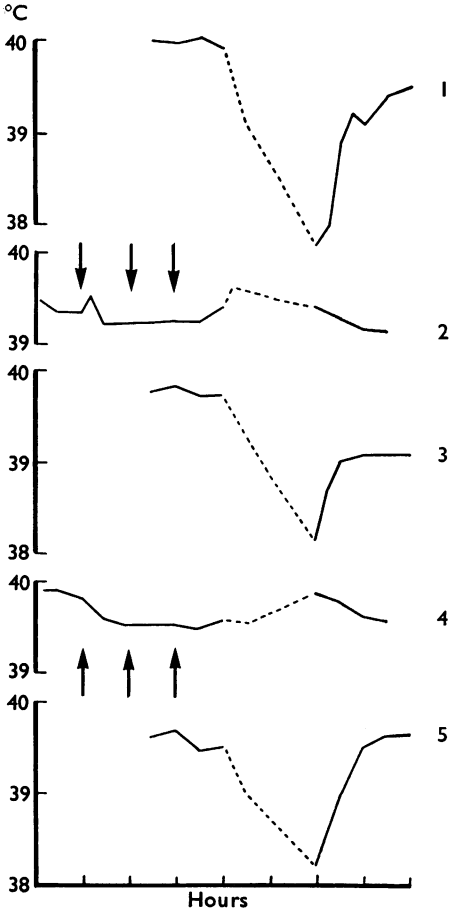

FIG. 2. Records of rectal temperature from a 2·9 mg cat obtained on different days. The interrupted lines indicate a 2 hr period of halothane inhalation and the arrows injections of 2 mg pheniprazine given either intraventricularly (record 2) or intraperitoneally (record 4). Record 3 obtained 24 hr after record 2, and record 5, 24 hr after record 4. Same experiment as the last one in Table 1.

by the intraventricular injections, but that it was reduced in two of the three experiments with the intraperitoneal injections.

The large rise in temperature beyond the pre-anaesthesia level after discontinuation of halothane anaesthesia as obtained with intraventricular tranylcypromine in one experiment (see Fig. 1) was not observed after the pheniprazine injections.

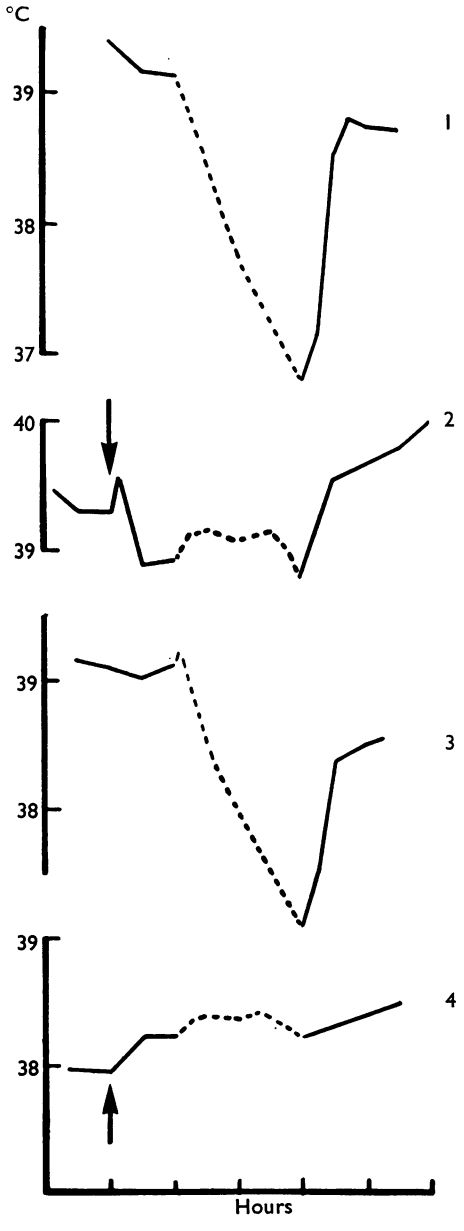

FIG. 3. Records of rectal temperature from a 2·8 kg cat obtained on different days. The interrupted lines indicate a 2 hr period of halothane inhalation and the arrows injections of 1 mg amphetamine given either intraventricularly (record 2) or intraperitoneally (record 4). Record 3 obtained 24 hr after record 2.

Pargyline

Summers (1969) found that intraperitoneal administration of pargyline in a dose of 50 mg/kg prevented the hypothermia of halothane inhalation and in a dose of 200 mg/kg caused a rise in temperature which became accentuated by the inhalation. These doses of pargyline are too large to be injected intraventricularly in a volume of 0·1 ml. On the other hand, smaller doses, 5 to 20 mg, injected intraventricularly or intraperitoneally were found not to affect the hypothermia of halothane inhalation given 1 hr later. Nor was the hypothermia affected by intraventricular or intraperitoneal injections of 5 mg given three times, or 20 mg given twice at hourly intervals, the last injection being given 1 hr before the inhalation. It was thus not possible to compare the efficacy of intraventricular and intraperitoneal injections of pargyline. Its ability to prevent the hypothermia was, however, confirmed with intraperitoneal injections of larger doses (150 to 200 mg) which by themselves did not cause the temperature to rise.

Amphetamine

Like the MAO inhibitors, amphetamine prevented the hypothermia of a halothane inhalation. The effect was obtained with intraperitoneal and intraventricular injections and with doses which by themselves scarcely affected temperature. Typical results obtained with 1 mg amphetamine are illustrated in Fig. 3.

Record 1 shows a fall of a little over 2° C during a 2 hr period of halothane inhalation. The fall did not occur when the inhalation was preceded, 1 hr earlier, by an intraventricular injection of 1 mg amphetamine. This is shown in record 2.

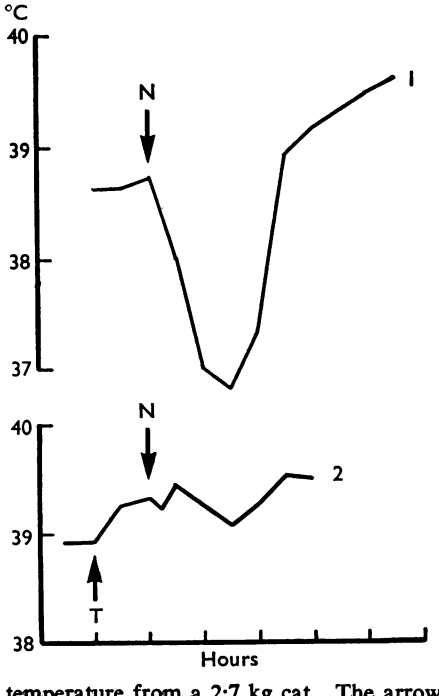

FIG. 4. Records of rectal temperature from a 2·7 kg cat. The arrows (N) indicate intraventricular injections of 200 μg noradrenaline and the arrow (T) intraperitoneal injection of 5 mg/kg tranylcypromine.

The amphetamine injection itself produced tachypnoea, dilatation of the ear vessels and a transient rise in temperature followed by a slight fall, effects usually obtained with intraventricular amphetamine. Record 3 shows that 24 hr after the intraventricular injection, halothane inhalation resulted again in a fall. Record 4 finally illustrates the effect of an intraperitoneal injection of 1 mg. Hypothermia did not occur during the halothane inhalation, which began one hour after the injection and which itself produced a slight rise in temperature (0·2° C). The other effects usually observed following an intraventricular injection of 1 mg amphetamine did not occur on its intraperitoneal injection.

Amphetamine was not more effective on intraventricular than on intraperitoneal injection ; on the contrary, in a few experiments the reverse was found. An injection of 0·2 mg given intraperitoneally or intraventricularly did not affect the halothane hypothermia. An injection of 0·5 mg tested in three cats reduced the hypothermia in two when given intraperitoneally, and in one when given intraventricularly. An injection of 1 mg regularly reduced the hypothermia with either route of injection, but sometimes the intraperitoneal route was more effective.

MAO inhibitors and amphetamine on hypothermia produced by intraventricular noradrenaline

MAO inhibitors

Tranylcypromine as well as pargyline injected intraperitoneally in doses which abolish the hypothermic effect of halothane or pentobarbitone anaesthesia, greatly reduced or abolished the temperature lowering effect of noradrenaline. This is illustrated in Figs. 4 and 5. The cat of experiment Fig. 4 responded to an intra-

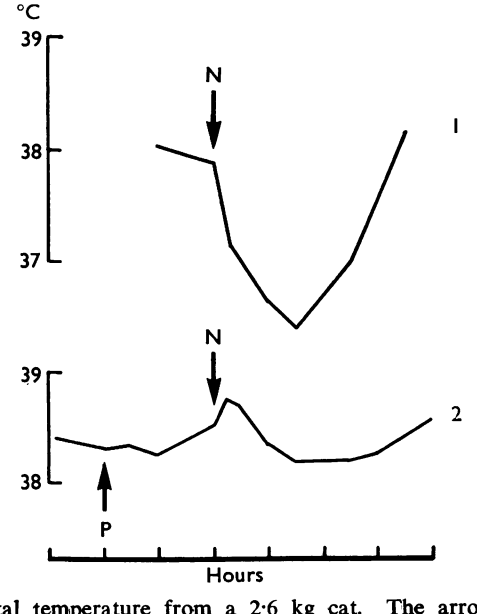

FIG. 5. Records of rectal temperature from a 2·6 kg cat. The arrows (N) indicate intraventricular injections of 200 μg noradrenaline, and the arrow (P) indicates intraperitoneal injections of 200 mg pargyline.

ventricular injection of 200 μg noradrenaline with a fall in temperature of about 2° C (record 1), but the same dose of noradrenaline given intraventricularly on another day, 1 hr after an intraperitoneal injection of tranylcypromine (5 mg/kg), caused a fall of 0·35° C only. The cat of experiment Fig. 5 responded to 200 μg noradrenaline with a fall of 1·5° C, but 1 hr after an intraperitoneal injection of 200 mg pargyline with a fall of 0·3° C only.

Amphetamine

The fall in temperature produced by intraventricular injections of noradrenaline was prevented or greatly reduced following intraperitoneal or intraventricular injections of amphetamine. In the experiment of Fig. 6, the cat responded to an intraventricular injection of 200 μg noradrenaline with a fall of nearly 2° C (record 1), but the fall was less than half a degree when the noradrenaline injection was preceded by three intraventricular or intraperitoneal injections of 1 mg amphetamine (records 2 and 3).

Discussion

The ability of the MAO inhibitors to prevent the hypothermia of anaesthesia in cats has been confirmed, but the explanation originally given requires some modification without, however, invalidating the theory that the hypothermia results from an action of noradrenaline released by the anaesthetics in the anterior hypothalamus. It was assumed that the inhibitors act on the MAO in the anterior hypothalamus and thus increase the concentration of the released 5-HT which would then be able to overcome the fall in temperature produced by the noradrenaline.

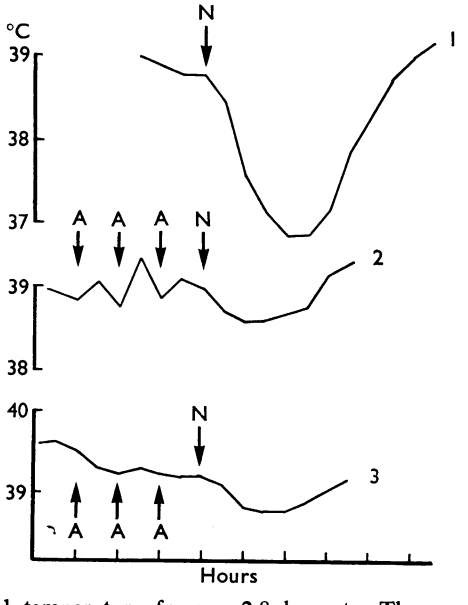

FIG. 6. Records of rectal temperature from a 2·8 kg cat. The arrows (N) indicate intraventricular injections of 200 μg noradrenaline and the arrows (A) injections of 1 mg amphetamine given either intraventricularly (record 2) or intraperitoneally (record 3).

From the comparison of the potency of intraperitoneal and intraventricular injections of the MAO inhibitors it was evident that when injected intraventricularly the inhibitors did not act by penetrating the walls of the third ventricle. To produce their effect they apparently first had to be absorbed into the blood stream ; otherwise, they should have been effective in smaller doses on intraventricular injection. If there was any difference, however, they were slightly more potent when injected intraperitoneally. It is easily forgotten how well substances can be absorbed from the liquor spaces. Although no experiments have been carried out on the absorption of the MAO inhibitors themselves, the absorption of histamine from the liquor spaces has been extensively studied and was found to be nearly half as rapid as from the subcutaneous tissue (Bhawe, 1958 ; Draskoci, Feldberg, Fleischhauer & Haranath, 1960 ; Feldberg, 1963). If the MAO inhibitors have first to be absorbed into the blood stream, even when injected intraventricularly, before they can prevent the hypothermia of a halothane anaesthesia, this does not exclude an action on the anterior hypothalamus. In favour of an action on this region of the brain is the finding that MAO inhibitors increase the 5-HT output from the perfused third ventricle of the cat when injected intraperitoneally (El Hawary *et al.*, 1967 ; Goodrich, 1969). If the effect were solely due to an action on the anterior hypothalamus it would however be difficult to understand why the intraventricular were not more effective than the intraperitoneal injections. The MAO inhibitors may thus produce their effect by acting on other brain stem regions as well, and even on the spinal cord. Even a peripheral action cannot be excluded, because MAO inhibitors are known to have peripheral actions. For instance, the profuse salivation which occurs in dogs in response to large doses of intraperitoneal tranylcypromine is a peripheral effect since it is not abolished by cutting both the chorda tympani and the cervical sympathetic (Feldberg, Hellon & Lotti, 1967). Furthermore, large doses of intravenous tranylcypromine in rabbits constrict the ear vessels and raise body temperature. This skin vasoconstriction, which is at least in part responsible for the rise in temperature, is also a peripheral effect as it occurs after cutting the cervical sympathetic (Rosendorff, 1969). If MAO inhibitors in doses too small by themselves to constrict the vessels were able to prevent the inhibition of vasoconstrictor tone produced by a central action of the anaesthetics, or if the anaesthetics were to render the skin vessels more sensitive to the vasoconstrictor action of the inhibitors, it would be possible to explain their ability to prevent the hypothermic effect of anaesthetics by a peripheral action. The same considerations apply to the results obtained with intraventricular and intraperitoneal injections of amphetamine which prevented the hypothermia of a halothane inhalation in doses too small to affect temperature by themselves.

The finding that amphetamine prevented the hypothermia of a halothane inhalation raises the question whether this effect when produced by MAO inhibitors which, like tranylcypromine and pheniprazine, have strong amphetamine-like actions (Goldberg & Sjoerdsma, 1959 ; Kinross-Wright, 1959 ; Spencer, 1960 ; Lee, Shin & Shideman, 1961) is an amphetamine-like effect and not the result of MAO inhibition. On the other hand, pargyline, which is known to have no amphetamine-like action (Goldberg, 1964), prevented the hypothermia as well. Both mechanisms may therefore be involved, otherwise one would have to postulate for pargyline, too, an amphetamine-like action at the adrenergic synapses in the anterior hypothalamus, or elsewhere in the central nervous system. The other possibility that the effect of

amphetamine itself is due to MAO inhibition, though not fully excluded, is unlikely because in *in vivo* experiments amphetamine was found not to inhibit the brain MAO (Pletscher & Gey, 1959).

Another observation made in the present experiments which is pertinent to the mechanism of action of the MAO inhibitors is their ability to prevent the hypothermia produced by an intraventricular injection of noradrenaline, an effect shared by amphetamine. The MAO inhibitors may render the anterior hypothalamus insensitive to the temperature lowering effect of noradrenaline and this may be the ultimate reason why they prevent the hypothermia produced by anaesthetics. It may again be an amphetamine-like effect, or an effect of the abnormal amounts of 5-HT persisting at the synapses after the enzymic inhibition. The mechanism of MAO inhibitors in preventing the hypothermia of anaesthesia is thus not yet fully understood.

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