J. Pharm. Pharmac., 1974, **26**, 335–343 *Received October* 26, 1973

The effect of monoamine oxidase inhibitors on the rectal temperature of the rat

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The monoamine oxidase (MAO) inhibitors, clorgyline, harmaline, nialamide, phenelzine and tranylcypromine, injected intraperitoneally into conscious unrestrained rats produced hypothermia. When clorgyline and tranylcypromine were compared, the latter produced a larger degree of hypothermia in spite of the fact that both drugs almost completely inhibited liver and hypothalamic MAO. Hypothermia produced by tranylcypromine, but not that produced by clorgyline, was attenuated by prior administration of haloperidol which indicated that it was partly mediated by a dopaminergic mechanism. In addition, tranylcypromine, but not clorgyline, inhibited uptake of (−)-noradrenaline into rat hearts. Hypoglycaemia was not involved in the hypothermia produced by these MAO inhibitors in rats.

The effect of monoamine oxidase inhibitors on body temperature varies according to the species, the inhibitor used and the route of administration (Feldberg, 1968; Summers, 1973a). In rats most reports indicate that the inhibitors produce hypothermia, whether given intraperitoneally (Goldwurm & Torrigiani, 1962; Schmidt & Fahse, 1964; Feldberg & Lotti, 1967; Bruinvels & Sourkes, 1968) or by injection into a lateral cerebral ventricle (Feldberg & Lotti, 1967). Furthermore, the inhibitor tranylcypromine was found to be effective in smaller doses when given intraventricularly which indicated a central rather than a peripheral action (Feldberg & Lotti, 1967).

The findings are not entirely consistent since it has been shown that nialamide has no effect and phenelzine produces a rise in temperature when given intraperitoneally (Schmidt & Fahse, 1964). It was suggested on the basis of these results that the effect of inhibitors on body temperature is not related to MAO inhibition or to the basic chemical structure of the inhibitors. In the same series of experiments, harmaline, harmine, pheniprazine and pargyline (MO911) produced hypothermia.

It has also been suggested that the effect of tranylcypromine could be due to inhibition of MAO, leading to a potentiation of the effects of the monoamines 5-hydroxytryptamine (5-HT) and noradrenaline in the hypothalamus, or alternatively to a direct 5-HT-like action of the inhibitor (Feldberg & Lotti, 1967; El Hawary, Feldberg & Lotti, 1967). Hypothermia would almost certainly result since both 5-HT and noradrenaline produce this effect when injected intraventricularly (Feldberg & Lotti, 1967; Myers & Yaksh, 1968). An effect on dopamine metabolism could also be involved since Kruk (1972) has shown that dopamine, a dopamine releaser, amphetamine, and a dopamine receptor agonist, apormorphine, produce hypothermia when given intraventricularly to rats. The effect is prevented by prior administration of the dopamine receptor blocking compound pimozide.

I have investigated whether the hypothermic effect is consistent with an inhibition of MAO in the hypothalamus and also whether the effect of tranylcypromine is the

result of an action on 5-HT metabolism, catecholamine metabolism or due to a direct action of the inhibitor. A preliminary account of some of the results has been published (Summers, 1973b).

METHODS

Temperature recording

Rectal temperature was measured in male Wistar rats (180–250 g) by means of thermistors (Radiospares TH-B12) inserted 5 cm into the rectum and taped to the base of the tail. The output of a conventional Wheatstone's bridge circuit was displayed on a Leeds-Northrup Speedomax W potentiometric dotting recorder. As restraint may affect temperature responses (Grant, 1950; Myers & Yaksh, 1968), recordings were taken from conscious unrestrained rats. Rectal thermistors were connected via a two-way connector to a miniature jack plug, which was free to move round in its socket whilst remaining in electrical contact with the thermistor. The first 20 cm of light hearing aid cable from the connector was protected by an extended light spring cemented to the connector. The rats were allowed to roam freely around a large polypropylene cage (40 × 25 × 15 cm). Continuous temperature recordings for up to 10 h were made using this method.

Environmental temperature in the laboratory varied between 20 and 24°. Experiments were always started between 8.30 and 9.30 a.m. to ensure that diurnal variations in temperature were constant.

Monoamine oxidise (MAO) activity

(a) *Preparation of tissues.* Rats were stunned and bled. The brain was removed and cooled to 0°. The hypothalamic area was removed from the brain as described by Iversen & Glowinski (1966) and homogenized in 10 vol of buffer (sucrose 0·25M, tris 0·05M, pH 7·4) in a Teflon/glass homogenizer. Slices of liver were removed and treated similarly.

(b) *Measurement of enzyme activity.* MAO activity of homogenates was determined by a modification of the method of Otsuka & Kobayashi (1964) using [^{14}C] tyramine as substrate. Metabolites formed during incubation for 1 h at 37° were extracted into toluene (shaking, 10 min), the layers separated by centrifugation (3100 *g*, 5 min). The organic layer was removed after leaving both layers overnight at −20° and was added to 10 ml of Butyl PBD Scintillant in toluene–2-methoxyethanol (4 : 1) and counted in a Packard Tri-carb Scintillation Counter. Boiled enzyme blank corrections were applied.

The method of McCaman, McCaman & others (1965) was used to measure activities with [^{14}C]5-HT as substrate.

Blood glucose determination

Rats were stunned, decapitated and a 0·1 ml sample of blood pipetted into 1 ml of uranyl acetate solution. The deproteinized blood was spun at 3100 *g* for 5 min and 0·05 ml of the supernatant used for the determination by the GOD-Perid method (Boehringer kit). Colorimetric measurements were made on a Bausch and Lomb colorimeter at a wavelength of 420 nm.

Noradrenaline uptake

Rat hearts were isolated and perfused with double glucose Krebs solution as described by Iversen (1963). A pulse of 0·5 μg of (—)-[^{3}H]noradrenaline was given into a fine polyethylene tube (Portex pp25) the tip of which terminated in the aortic cannula. Five min later the amount of amine retained by the heart was determined by weighing and homogenizing the heart in isopropanol–water (1 : 1) using a Polytron homogenizer. 1 ml aliquots of homogenate were added to 10 ml of Instagel (Packard Inst. Inst. SA), gently shaken and counted as before. Corrections were made for blanks and for quenching. Drugs were dissolved in the Krebs perfusion medium.

Drugs

Clorgyline hydrochloride (May and Baker Ltd.); nialamide (Pfizer Ltd.); harmaline (Fluka AG); phenelzine (W. Warner and Co. Ltd.); tranylcypromine (Smith, Kline and French Laboratories Ltd.); haloperidol (G. D. Searle and Co.); *p*-chlorphenylalanine (Koch-Light Laboratories Ltd.); soluble insulin (Boots Pure Drug Co.); [^{14}C]tyramine, [^{14}C]5-HT, (—)-[^{3}H]noradrenaline (Radiochemical Centre, Amersham).

In temperature experiments the water-soluble drugs were dissolved in sterile pyrogen-free 0·9% saline and injected with sterile syringes and needles. Harmaline and nialamide were dissolved in 0·1–0·2 ml dimethylsulfoxide (DMSO), added to 5 to 10 vol of pyrogen-free saline and injected as a milky suspension. The doses given refer to the salts.

Doses of MAO inhibitors

The doses of the MAO inhibitors, nialamide (Schoepke & Wiegand, 1963), clorgyline (Christmas, Coulson & others, 1972), harmaline (Udenfriend, Witkop & others, 1958), phenelzine (Christmas & others, 1972) and tranylcypromine (Green & Erikson, 1960), were chosen to give almost complete MAO inhibition, using 5-HT as substrate, within 1 h of injection. In the case of the irreversible inhibitors, nialamide (Pletscher, Gey & Butkard, 1966), clorgyline and phenelzine (Christmas & others, 1972), the inhibition would be expected to persist until the time of death 5 h after injection.

RESULTS

Temperature effects of MAO inhibitors

Each of the five inhibitors produced hypothermia in rats when injected intraperitoneally as shown in Fig. 1. Nialamide (25 mg kg^{-1}) and clorgyline (10 mg kg^{-1}) produced only small effects on temperature whereas harmaline (25 mg kg^{-1}), phenelzine (50 mg kg^{-1}) and tranylcypromine (5 mg kg^{-1}) produced pronounced hypothermia. Injection of the DMSO/saline vehicle used to dissolve nialamide and harmaline produced no effect on temperature. In the case of phenelzine and occasionally with tranylcypromine, clorgyline and harmaline the injection of the drug was followed by a period during which there was vasodilatation of the blood vessels of the ears and tail which became pink and warm to the touch.

MAO activity

Rats were killed immediately after the temperature experiments and the hypothalamus and liver removed for MAO assay, using two substrates, tyramine and 5-HT.

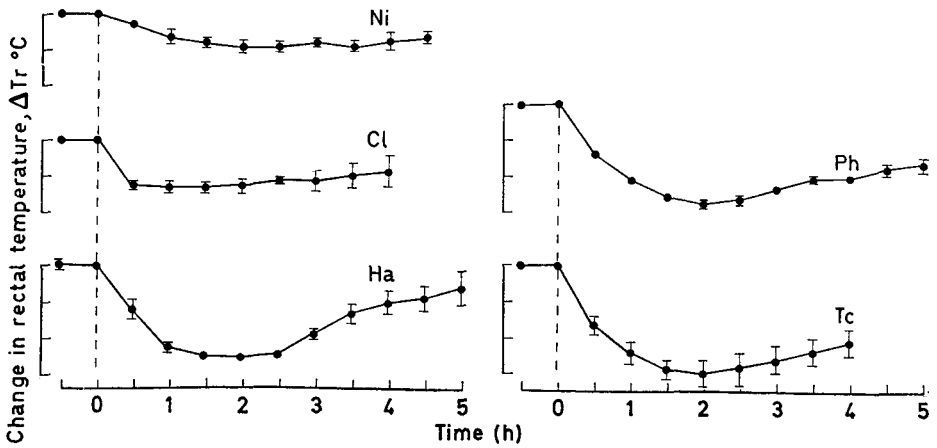

FIG. 1. Records of changes of rectal temperature (ΔTr °C) taken from rats injected intraperitoneally, at the dotted line, with MAO inhibitors. Ambient temperature 20–24°. Ni = nialamide (25 mg kg^{-1}, n = 4); Cl = clorgyline (10 mg kg^{-1}, n = 8); Ha = Harmaline (25 mg kg^{-1}, n = 5); Ph = phenelzine (50 mg kg^{-1}, n = 5); Tc = tranylcypromine (5 mg kg^{-1}, n = 8).

The results in Table 1 show that phenelzine (50 mg kg^{-1}), an inhibitor which is not substrate selective (Christmas & others, 1972), produced almost complete inhibition of MAO in both tissues with both substrates. The substrate selective inhibitor clorgyline (10 mg kg^{-1}) (Christmas & others, 1972) inhibited 5-HT much more than tyramine oxidation. Nialamide (25 mg kg^{-1}) inhibited MAO activity in the liver more than in the hypothalamus. This relative lack of inhibitory effect in the hypothalamus could explain the relatively weak hypothermic effect of nialamide.

Table 1. *Effects of MAO inhibitors on MAO activity in the hypothalamus and liver of the rat.*

Dose of MAOI mg kg^{-1}, i.p.		MAO activity expressed as a % of control values: Tyramine substrate, Hypothalamus	Tyramine substrate, Liver	5-HT substrate, Hypothalamus	5-HT substrate, Liver
Control (saline injected)		100 ± 4·26 (10)	100 ± 5·82 (10)	100 ± 8·92 (10)	100 ± 5·30 (10)
Clorgyline	0·01	101·52 ± 4·54 (5)	80·41 ± 3·22 (6)	91·50 ± 8·75 (6)	118·97 ± 5·92 (6)
	0·1	49·76 ± 8·60 (6)	68·87 ± 7·76 (6)	16·25 ± 4·53 (6)	94·70 ± 3·02 (5)
	2	27·98 (2)	47·02 (2)	2·06 (2)	47·6 (2)
	10	29·00 ± 1·13 (4)	28·30 ± 2·19 (4)	1·91 ± 0·27 (4)	7·99 ± 0·61 (4)
Nialamide	25	46·90 ± 0·81 (4)	7·88 ± 0·72 (4)	39·70 ± 1·34 (4)	2·73 ± 0·65 (4)
Harmaline	25	88·91 ± 4·37 (4)	82·11 ± 9·13 (4)	31·72 ± 5·05 (4)	31·66 ± 8·88 (4)
Phenelzine	50	5·24 ± 0·52 (4)	3·21 ± 0·12 (4)	2·04 ± 0·53 (4)	1·74 ± 0·21 (4)
Tranylcypromine	5	15·01 ± 1·90 (4)	8·18 ± 1·23 (4)	7·11 ± 1·11 (4)	7·13 ± 0·38 (4)

Tranylcypromine is an example of a non-selective (Christmas & others, 1972) and partially reversible inhibitor (Pletscher & others, 1966) and this is reflected in the results in Table 1. Enzyme activities against both substrates were similar but there was a small amount of activity measurable 5 h after administration of the drug. Harmaline is reversible (Udenfriend & others, 1958) and selective (Chodera, Gorkin & Gridneva, 1964) for 5-HT metabolism, and indeed after 5 h the enzyme activities approached normal and activity against tyramine recovered faster than that against 5-HT.

The experiments show that all the inhibitors produced a fall in rectal temperature and inhibition of MAO in the hypothalamus. Differences in the degree of hypo-

thermia were studied in more detail for two of the inhibitors clorgyline and tranylcypromine.

Comparison of the effects of clorgyline and tranylcypromine

It is now generally accepted that MAO is not one enzyme but several (Blaschko, Richter & Schlossman, 1937; Gorkin, 1963; Youdim, Collins & Sandler, 1968, 1969) and the effects of clorgyline were thought to be particularly interesting as it preferentially inhibits the MAO concerned with 5-HT metabolism (Johnson, 1968; Squires, 1968; Hall, Logan & Parsons, 1969; Jarrott, 1971; Christmas & others, 1972).

Substrate and tissue selectivity were shown by clorgyline *in vivo*. Fig. 2 shows the effect of three dose levels of clorgyline on temperature. 0·1 mg kg^{-1} had little effect on temperature but did inhibit MAO to some extent particularly in the hypothalamusi 5-HT metabolism in liver and tyramine metabolism in hypothalamus and liver were much less affected (Table 1).

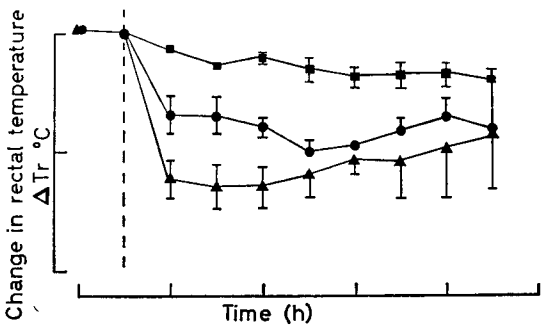

FIG. 2. Effect of intraperitoneal injection of clorgyline, 0·1 mg kg^{-1} (■, n = 4), 2 mg kg^{-1} (●, n = 4), and 10 mg kg^{-1} (▲, n = 8) on rectal temperature in the rat.

Clorgyline (2 mg kg^{-1} n = 4) produced the characteristically small but definite hypothermia compared with the lower dose ($P < 0.05$; 30–180 min) and almost completely inhibited 5-HT metabolism in the hypothalamus. Again 5-HT metabolism in the liver and tyramine metabolism in the hypothalamus and liver were less affected. In the lower record 10 mg^{-1} clorgyline (n = 8) had no significantly larger effect on temperature and only significantly reduced 5-HT metabolism in the liver (7·99 ± 0·61 % n = 4) compared with 0·1 or 2 mg kg^{-1} clorgyline.

In spite of the fact that clorgyline completely inhibited 5-HT metabolizing activity in the hypothalamus it produced a smaller degree of hypothermia than tranylcypromine. This suggested that tranylcypromine does not produce hypothermia only by MAO inhibition. Support for this view is shown in Fig. 3. In Fig. 3a, 10 mg kg^{-1} clorgyline produced hypothermia, then after 1 h tranylcypromine (5 mg kg^{-1}) was given and produced a further steep fall of temperature. It is unlikely that this effect of tranylcypromine is due to MAO inhibition since over this period of time the clorgyline injection would irreversibly inhibit the enzyme. A second dose of clorgyline given 1 h after the first had no further effect on temperature (Fig. 3b), neither did a dose of clorgyline given after tranylcypromine (Fig. 3c). Therefore it seems likely that tranylcypromine has other properties that significantly contribute to its temperature lowering effect while clorgyline produces its effect solely by MAO inhibition.

Role of dopamine in the temperature response to tranylcypromine

The amphetamine-like properties of tranylcypromine are well-known (Feldberg &

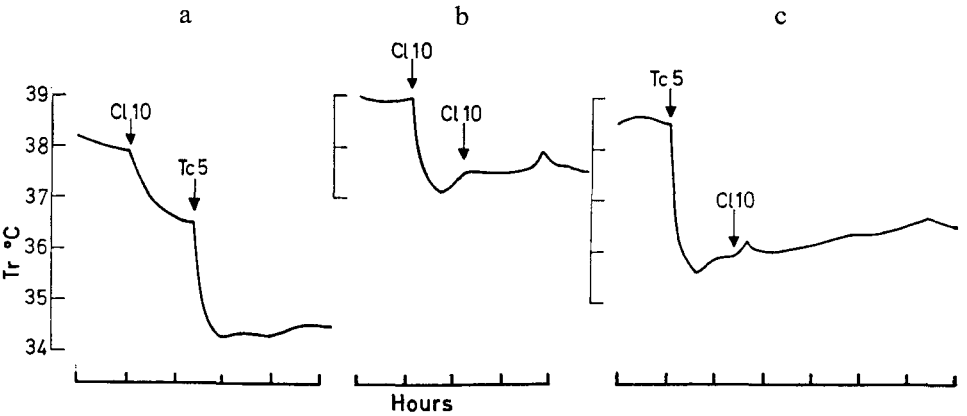

FIG. 3. Records of rectal temperature (Tr °C) from rats injected with clorgyline (10 mg kg^{-1} i.p.) and tranylcypromine (5 mg kg^{-1} i.p.) at the arrows.

Lotti, 1967). Amphetamine can produce hypothermia by central release of dopamine (Yehuda & Wurtman, 1972; Kruk, 1972) and the effect is blocked by compounds that block dopamine receptors. It is possible, therefore, that part of the hypothermia produced by tranylcypromine is mediated by a dopamine-like mechanism. Tranylcypromine (Fig. 4a) (5 mg kg^{-1} i.p.) produced a fall of temperature (ΔTr max) of 3·01 $\pm$ 0·39° (n = 8) at 2 h, whereas clorgyline (10 mg kg^{-1} i.p.; Fig. 4b), which does not have amphetamine-like properties, produced a fall of only 1·29 $\pm$ 0·17° (n = 8; P <0·05). Hypothermia produced by tranylcypromine was attenuated by the dopamine receptor blocking agent haloperidol (0·5 mg kg^{-1} i.p.) given 1 h previously (Fig. 4c). Under these conditions Δ Tr max was reduced to 1·26 $\pm$ 0·08° (n = 4; P <0·02). The remaining hypothermia was indistinguishable from that produced by clorgyline (P >0·9). Responses to clorgyline were unaffected by pretreatment with haloperidol (n = 3; P >0·7).

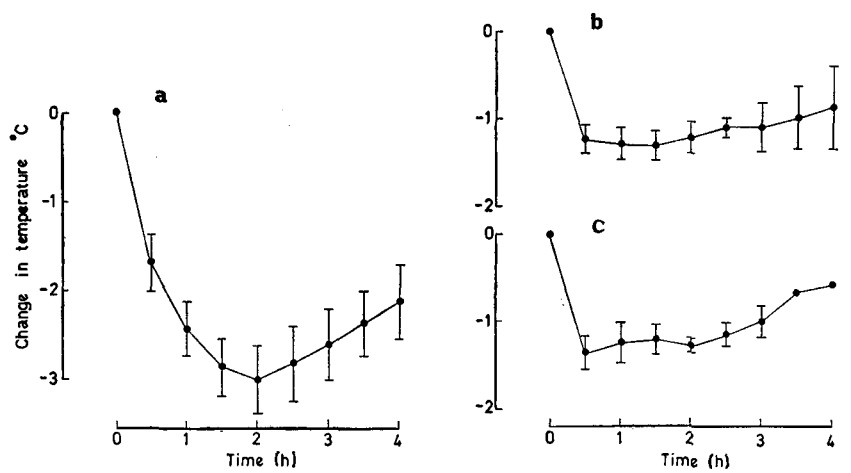

FIG. 4. Changes in rectal temperature (Δ Tr °C) produced by (a) tranylcypromine (5 mg kg^{-1} i.p.), (b) clorgyline (10 mg kg^{-1} i.p.) and (c) tranylcypromine (5 mg kg^{-1} i.p.) given after haloperidol (0·5 mg kg^{-1}).

Experiments with rats pretreated with p-*chlorphenylalanine* (*pCPA*)

Inhibition of 5-HT synthesis by pCPA (320 mg kg^{-1} i.p.) leads to a fall in brain

5-HT levels (Koe & Weissman, 1966; Oka, Nozaki & Hosoya, 1972). If the effect of MAO inhibitors is mediated through potentiation of the central effects of 5-HT, pCPA pretreatment might be expected to reduce the response.

Forty eight h after pCPA (320 mg kg^{-1} i.p.) rats were very lively and often aggressive. At ambient temperatures of 20–24° their body temperatures were within the normal range. pCPA treatment had little effect on temperature responses to inhibitors; hypothermia to tranylcypromine (2 rats) or clorgyline (4 rats) was indistinguishable from that in control experiments.

MAO inhibitors and blood glucose

In mice, tranylcypromine is known to increase the secretion of insulin and produce hypoglycaemia (Bressler, Vargas-Cordon & Lebovitz, 1968). The effect is apparently mediated through β-adrenoceptors since it can be prevented by β-adrenoceptor blocking drugs. Insulin hypoglycaemia in mice results in hypothermia (Robinson, Mager & Freinkel, 1973) so that a hypoglycaemic effect of tranylcypromine in the rat could play a part in the production of hypothermia.

Injections of saline (control group), or drugs, were given intraperitoneally 1 h before blood samples were taken. Tranylcypromine (5 mg kg^{-1}) or clorgyline (10 mg kg^{-1}) treatment had no significant effect on the levels, whereas soluble insulin (20 iu kg^{-1}) produced profound hypoglycaemia ($P < 0{\cdot}001$)* and the effect was associated with a small progressive fall in temperature quite different from that produced by the inhibitors. Therefore, hypoglycaemia did not appear to be involved in the production of hypothermia to MAO inhibitors in rats.

MAO inhibitors and noradrenaline uptake

Tranylcypromine is known to affect the release and uptake of catecholamines (Iversen, 1967; von Euler, 1970). The effect of clorgyline on these processes does not appear to have been studied.

To test for effects on uptake, rat hearts were prepared as described in Methods and a pulse of (−)-[^{3}H]noradrenaline injected into the cannula leading to the heart. Control hearts took up 24·0 $\pm$ 0·4 ng (n = 5), those perfused with a medium containing 10 μg ml^{-1} clorgyline took up 28·2 $\pm$ 2·8 ng (n = 4, ns), and those perfused with a medium containing 5 μg ml^{-1} tranylcypromine took up 5·7 $\pm$ 0·5 ng (n = 4, $P < 0{\cdot}05$) of labelled noradrenaline.

In addition, hearts perfused with a medium containing tranylcypromine, but not the controls or those with clorgyline, showed an increased rate and force of contraction, illustrating the well-known sympathomimetic activity of this inhibitor. Since it is known that intraventricular noradrenaline produces hypothermia in rats, central release and prevention of uptake of this amine by tranylcypromine could be a contributory factor in the hypothermia produced by this drug.

DISCUSSION

The inhibitors produced hypothermia which varied in magnitude. Results with harmaline and tranylcypromine agree with those of previous investigators (Gunn, 1909; Zettler, 1957; Goldwurm & Torrigiani, 1962; Schmidt & Fahse, 1964; Feldberg

*Control 88·6 $\pm$ 2·8 mg%; tranylcypromine 91.0 $\pm$ 2·0% ($P > 0{\cdot}4$); clorgyline 91.5 $\pm$ 2·6 mg% ($P > 0{\cdot}5$); insulin (201u kg^{-1}) 35·0 $\pm$ 3·3% ($P < 0{\cdot}001$).

& Lotti, 1967; Bruinvels & Sourkes, 1968). Nialamide (25 mg kg^{-1}) and phenelzine (50 mg kg^{-1}) also produced hypothermia whereas Schmidt & Fahse (1964) found that larger doses of nialamide (100 mg kg^{-1}) had no effect and phenelzine (100 mg kg^{-1}) produced hyperthermia. The small or absent effect of nialamide could be explained by the observation that this drug inhibited liver MAO much more effectively than the hypothalamic enzyme. Phenelzine (50 mg kg^{-1}) on the other hand produced complete inhibition of liver and hypothalamic MAO so that the reversal seen with higher doses may reflect a toxic hyperthermic effect unrelated to MAO inhibition.

Most of the evidence suggests that the inhibitors produce hypothermia by a central action. Tranylcypromine is effective in smaller doses when given intraventricularly (Feldberg & Lotti, 1967) and the present experiments show that five inhibitors produced hypothermia and enzyme inhibition in the hypothalamus. In experiments in which temperature was returning to normal at the time of death MAO activity wasalso returning. Apparently, return of only a small amount of enzyme activity enables it to fulfil its physiological function (Pletscher & Zeller, 1960).

The most interesting inhibitor used was clorgyline. This substrate-specific inhibitor produces a much smaller degree of hypothermia than tranylcypromine yet completely inhibited 5-HT metabolizing activity in the hypothalamus. Experiments using both tranylcypromine and clorgyline strongly suggest that the former possesses properties unrelated to MAO inhibition which contribute to its temperature-lowering effect (probably release of the hypothermic amine dopamine, since part of the hypothermia is blocked by pretreatment of rats with haloperidol).

The remaining hypothermia and that produced by clorgyline is probably due to potentiation of the actions of the central transmitters 5-HT or noradrenaline as a result of MAO inhibition. 5-HT could be involved in the response since it is known to produce hypothermia when given intraventricularly to rats (Feldberg & Lotti, 1967), is present in a high concentration in the anterior hypothalamus (Quay & Halevy, 1962) and has a rapid rate of turnover. The rise in 5-HT levels and the hypothermia both begin a few minutes after injection of the rapidly acting MAO inhibitors suggesting on a temporal basis that this amine could be involved. However, depletion of 5-HT by pCPA had no effect on the hypothermia produced by clorgyline and tranylcypromine. This could be countered by the suggestion that normal transmitter functions can be carried out by the small amount of remaining amine (Myers, 1970).

Noradrenaline is capable of producing both hypo- and hyperthermia when given intraventricularly (Feldberg & Lotti, 1967; Myers & Yaksh, 1968). Its turnover rate in the hypothalamus is slow, about 4 h (Iversen & Glowinski, 1966), so that a slow increase of levels and of onset of response might be expected. In addition its actions are terminated by uptake and by the enzyme catechol-*O*-methyl transferase (COMT). It is, therefore, unlikely that the actions of noradrenaline would be greatly potentiated by MAO inhibition alone. However, some inhibitors of MAO, such as tranylcypromine, are also potent inhibitors of noradrenaline uptake so that potentiation of the actions of noradrenaline could be a factor in the production of hypothermia by these inhibitors.

Hypoglycaemia did not seem to be involved in the production of hypothermia in rats since neither tranylcypromine nor clorgyline in doses that produced hypothermia had an effect on blood sugar levels. Insulin, however, produced profound hypoglycaemia and a small fall in temperature quite unlike that produced by the MAO inhibitors.

In conclusion, the MAO inhibitors produce hypothermia in the rat. The effects of one, tranylcypromine, are partly due to properties unrelated to MAO inhibition whereas those of another, clorgyline, appear to be the result of a relatively specific enzyme inhibition and this drug may prove to be a useful tool for the examination of the temperature effects of central MAO inhibition.

REFERENCES

BLASCHKO, H., RICHTER, D. & SCHLOSSMAN, H. (1937). *Biochem. J.*, **31**, 2187–2196.

BRESSLER, R., VARGAS-CORDON, M. D. & LEBOVITZ, H. E. (1968). *Diabetes*, **17**, 617–624.

BRUINVELS, J. & SOURKES, T. L. (1968). *Eur. J. Pharmac.*, **4**, 31–39.

CHODERA, A., GORKIN, V. Z. & GRIDNEVA, L. I. (1964). *Acta biol. med. germ.*, **13**, 101–109.

CHRISTMAS, A. J., COULSON, C. J., MAXWELL, D. R. & RIDDELL, D. (1972). *Br. J. Pharmac.*, **45**, 490–503.

EL HAWARY, M. B. E., FELDBERG, W. & LOTTI, V. J. (1967). *J. Physiol., Lond.*, **188**, 131–140.

EULER, U. S. VON (1970). Bayer Symposium 11, p. 144, Springer, Berlin.

FELDBERG, W. (1968). *Recent advances in pharmacology*, 4th edn, p. 349–397. London: Churchill.

FELDBERG, W. & LOTTI, V. J. (1967). *Br. J. Pharmac. Chemother.*, **31**, 152–161.

GOLDWURM, G. F. & TORRIGIANI, G. (1962). *Minerva Med. (Torino)*, **53**, 2266–2268.

GORKIN, V. Z. (1963). *Nature*, **200**, 77.

GRANT, R. (1950). *Am. J. Physiol.*, **160**, 285–290.

GREEN, H. & ERIKSON, R. W. (1960). *J. Pharmac. exp. Ther.*, **129**, 237–242.

GUNN, J. A. (1909). *Trans. R. Soc. Edinb.*, **47**, 245.

HALL, D. W. R., LOGAN, B. W. & PARSONS, G. H. (1969). *Biochem. Pharmac.*, **18**, 1447–1454.

IVERSEN, L. L. (1963). *Br. J. Pharmac. Chemother.*, **21**, 523–537.

IVERSEN, L. L. (1967). *The uptake and storage of noradrenaline in sympathetic nerves.* Cambridge University Press.

IVERSEN, L. L. & GLOWINSKI, J. (1966). *J. Neurochem.*, **13**, 671–682.

JARROTT, B. (1971). *Ibid.*, **18**, 7–16.

JOHNSON, J. P. (1968). *Biochem. Pharmac.*, **17**, 1285–1297.

KOE, B. K. & WEISSMAN, A. (1966). *J. Pharmac. exp. Ther.*, **154**, 499–516.

KRUK, Z. L. (1972). *Life Sci.*, **11**, Part 1, 845–850.

MCCAMAN, R. E., MCCAMAN, M. W., HUNT, J. M. & SMITH, M. S. (1965). *J. Neurochem.*, **12**, 15.

MYERS, R. D. (1970). *Physiological and behavioural temperature regulation*, p. 655, Editor: Hardy, J. D. Springfield: Charles Thomas.

MYERS, R. D. & YAKSH, T. L. (1968). *Physiol. Behav.*, **3**, 917.

OKA, T., NOZAKI, M. & HOSOYA, E. (1972). *J. Pharmac. exp. Ther.*, **180**, 136–143.

OTSUKA, S. & KOBAYASHI, Y. (1964). *Biochem. Pharmac.*, **13**, 995–1006.

PLETSCHER, A. & ZELLER, P. (1960). *Progress in drug research*, vol. 2, p. 417. Editor: Jucker, E. Basel: Birkhäuser.

PLETSCHER, A., GEY, K. F. & BURKARD, W. P. (1966). *Handbook der experimentellen pharmakologie* XIX, Berlin: Springer.

QUAY, W. B. & HALEVY, A. (1962). *Physiol. Zool.*, **35**, 1–7.

ROBINSON, S. M., MAGER, M. & FREINKEL, N. (1973). *The pharmacology of thermoregulation*, pp. 112–123. Editors: Schonbaum, E. & Lomax, P. Basel: S. Karger.

SCHMIDT, J. & FAHSE, C. (1964). *Acta biol. med. germ.*, **13**, 607.

SCHOEPKE, H. G. & WIEGAND, R. G. (1963). *Ann. N.Y. Acad. Sci.*, **107**, 924–934.

SQUIRES, R. F. (1968). *Biochem. Pharmac.*, **17**, 1401–1409.

SUMMERS, R. J. (1973a). *The pharmacology of thermoregulation*, pp. 217–231. Editors: E. Schonbaum & P. Lomax. Basel: S. Karger.

SUMMERS, R. J. (1973b). *I.R.C.S.* (73–3), 7–4–1.

UDENFRIEND, S., WITKOP, B., REDFIELD, B. G. & WEISSBACH, H. (1958). *Biochem. Pharmac.*, **1**, 160–165.

YEHUDA, S. & WURTMAN, R. J. (1972). *Life Sci.*, **11**, Part 1, 851–859.

YOUDIM, M. B. H., COLLINS, G. G. S. & SANDLER, M. (1968). *Febs. Letters*, **1**, 215–218.

YOUDIM, M. B. H., COLLINS, G. G. S. & SANDLER, M. (1969). *Nature*, **223**, 626–628.

ZETTLER, G. (1957). *Arch. exp. Path. Pharmak.*, **231**, 34.