Monoamine Oxidase Inhibition in Brain and Liver of Rats Treated with Chlordimeform

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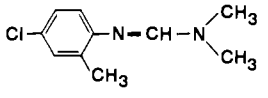
Chlordimeform is unique among the insecticidal and acaricidal agents in being the only substance of this type that inhibits monoamine oxidase (MAO). In an attempt to define this activity of the compound more precisely in vivo, its effects on biogenic amine metabolism in the rat brain were studied. The inhibition of MAO activity induced by chlordimeform in the rat liver and brain in vivo is dose related, but relatively large amounts (10–30 mg/kg) are required to produce a clear-cut effect. MAO is inhibited to a greater degree in the liver than in the brain: in both organs, type B MAO is affected more than type A, as is evident from the relative extents to which phenethylamine and serotonin are exempt from deamination. Like other MAO inhibitors, chlordimeform alters the metabolism of catecholamines and serotonin, although the endogenous levels of homovanillic acid are depressed much less than those of dihydroxyphenylacetic acid. In contrast to the MAO inhibitors used in human medicine, chlordimeform is a weak inhibitor and has a rather short duration of action, probably because its inhibitory effect is reversible.

Chlordimeform (Galecron, Fundal) is *N'*-(4-chloro-*o*-tolyl)-*N*,*N*-dimethylformamidine, the best characterized representative of a new chemical class of insecticidal and acaricidal agents. Its acaricidal activity is not a result of



Chlordimeform

the inhibition of acetylcholinesterase (Dittrich, 1966). Abo-Khatwa and Hollingworth (1972, 1973) reported that chlordimeform was an uncoupler of oxidative phosphorylation in mitochondria isolated from cockroach thoracic muscle and from rat liver; but it was soon recognized that the signs of intoxication shown by cockroaches exposed to chlordimeform were completely different from those seen after treatment with 2,4-dinitrophenol, a potent uncoupler of oxidative phosphorylation (Beeman and Matsumura, 1974). A further interaction with a biochemical process was described practically simultaneously by two groups of entomologists working independently of each other. Beeman and Matsumura (1973) described the inhibitory effect of chlordimeform on monoamine oxidase (MAO) activity in the rat liver, in vitro. They also demonstrated the inhibitory action on MAO of the N-demethylated analogue of chlordimeform, a metabolite normally formed in mammals and insects (Knowles et al., 1972). Almost identical results were reported a few weeks later by Aziz and Knowles (1973). Subsequent studies confirmed that chlordimeform had an inhibitory effect in vitro on MAO extracted from cockroach heads (Beeman and Matsumura, 1974) or from the cattle tick *Boophilus microplus* (Atkinson et al., 1974; Holden and Hadfield, 1975). Very recently, Benezet and Knowles (1976) presented evidence showing that chlordimeform and two of its metabolites competitively inhibit MAO in the rat brain in vitro.

The present experiments were undertaken to define the MAO inhibitory properties of chlordimeform in vivo in the rat brain and liver and to determine the consequent effects on the biosynthesis and catabolism of noradrenaline, dopamine, and serotonin. These amines are actually physiological substrates of MAO. Since they are known to participate in the regulation of central and peripheral nervous functions, alterations in their metabolism caused by chlordimeform might play a role in the specific acaricidal or the general toxic action of the compound.

METHODS

Male albino Sprague Dawley rats (170–210 g of body weight) were kept under constant lighting conditions (10 h light, 14 h darkness) and allowed food (Nafag 890) and water ad libitum. Male Wistar rats (180–220 g of body weight) were used in experiments in which the aromatic amino acid decarboxylase was inhibited by 3-hydroxybenzylhydrazine (NSD 1015). The animals were treated orally or intraperitoneally with chlordimeform, and groups of four were killed by decapitation at various times thereafter for estimations of MAO activity and of biogenic amines and amine metabolites.

MAO activity was determined by radioassay in the whole brain or in the liver, essentially as described by Wurtman and Axelrod (1963). ^{14}C-labeled 5-hydroxytryptamine binoxalate (5-HT; 48.5 mCi/mM, New England Nuclear, Boston, Mass.), ^{14}C-labeled tyramine (55 mCi/mM, The Radiochemical Centre, Amersham, Bucks.), and [^{14}C]-phenethylamine hydrochloride (PEA; 9.86 mCi/mM, New England Nuclear, Boston, Mass.) were used as substrates at a concentration of 6.25 nM (10 nCi) for a final incubation mixture of 0.3 mL. The ^{14}C-deaminated material formed after incubation for 20 min at 37 °C was extracted with 6 mL of ethyl acetate. Aliquots of 4 mL were counted together with 1 mL of ethanol and 10 mL of toluene containing 0.6% butyl-PBD [2-(4-butylphenyl)-5-(4-biphenylyl)-1,3,4-oxadiazole, Scintillator CIBA].

Homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were isolated from the corpus striatum according to the technique used by Murphy et al. (1969). HVA was determined fluorometrically by an automated procedure based on the method of Andén et al. (1963). DOPAC was determined fluorometrically as described by Sharman (1971). The estimations were made in four samples for the treated group and in six samples for the controls, each sample comprising four striata.

Noradrenaline (NA) and dopamine (DA) were extracted into 10% trichloroacetic acid, adsorbed on alumina at pH 8.6, eluted with 0.25 N HCl, and determined by automated fluorometry, as described in detail by Waldmeier et al. (1974).

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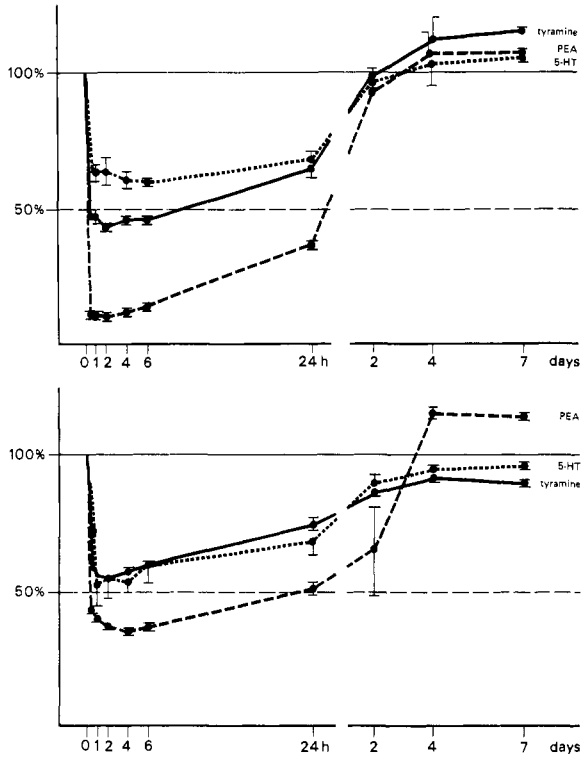

Figure 1. Time-course of the MAO-inhibitory effect of chlordimeform (100 mg/kg, i.p.) in the rat liver (upper panel) and brain (lower panel). Each plotted value represents $\bar{x} \pm S_{\bar{x}}$ ($n = 4$) in percent of controls.

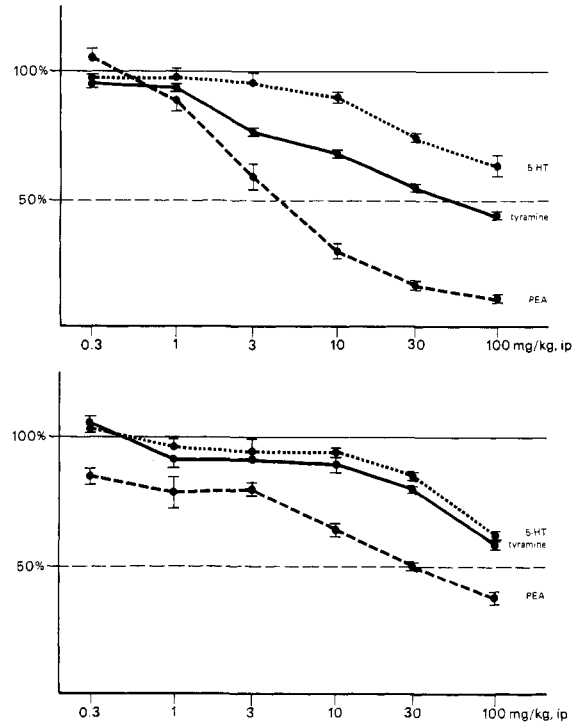

Figure 2. Relation between dose and MAO-inhibitory effect of chlordimeform in the rat liver (upper panel) and brain (lower panel). The organs were removed 2 h after treatment with chlordimeform. Each plotted value represents $\bar{x} \pm S_{\bar{x}}$ ($n = 4$) in percent of controls.

5-Hydroxytryptamine (5-HT) and its deaminated metabolite 5-hydroxyindoleacetic acid (5-HIAA) were analyzed fluorometrically by the method of Curzon and Green (1970).

After inhibition of the peripheral and central aromatic amino acid decarboxylase with 3-hydroxybenzylhydrazine (NSD 1015), the rat brains were extracted by treatment with 0.4 N perchloric acid and passage through a strongly cationic column, as described by Atack and Magnusson (1970) and Kehr et al. (1972), and then analyzed. Dihydroxyphenylalanine (DOPA), tyrosine (TYR), 5-hydroxytryptophan (5-HTP), tryptophan (TRY), NA, DA, and 5-HT were determined fluorometrically, as described earlier (Carlsson et al., 1972). In these studies, corpus striatum, limbic forebrain and hemispheres were dissected as described by Kehr et al. (1976). Each extract consisted of two pooled brain regions.

Statistical significance was calculated by means of the Student's t test with the exception of the results presented in Tables III and IV for which the Dunnett test was used.

RESULTS

Effect on MAO Activity. In one set of experiments, MAO activity was determined at various times after treatment in liver and whole brain from animals given chlordimeform in the very high dose of 100 mg/kg i.p. As is shown in Figure 1, MAO activity in both organs was depressed. Inhibition was already nearly maximal after 30 min and began to abate after 4–6 h. MAO activity reverted to normal after 2 days in the liver and after 2–4 days in the brain. MAO-B was inhibited more than MAO-A, as is evident from the rates of deamination of the different substrates: PEA deamination was antagonized to a greater extent than 5-HT deamination in both organs, but the difference was more pronounced in the liver than in the brain. To determine the dose–effect relations, estimations were made in organs removed 2 h after the intraperitoneal or oral administration of various doses of chlordimeform.

Table I. MAO Inhibition in the Rat Liver and Brain 2 h after Oral Treatment with Chlordimeform[a]

	ED_{50} in mg/kg		
	PEA	Tyramine	5-HT
Liver	5.5	30	>300
Brain	35	300	>300

[a] The figures quoted are ED_{50}'s, which were determined by graphical interpolation from experiments carried out as shown in Figure 2. Doses of 1, 3, 10, 100, and 300 mg were used. Each group consisted of four rats.

As can be seen from the results obtained after intraperitoneal administration (Figure 2), the MAO inhibitory effect of the substance is dose dependent. In the liver, the threshold dose is between 1 and 3 mg/kg and in the brain between 3 and 10 mg/kg. Clear-cut inhibition of MAO-A, however, as judged from the deamination of 5-HT, only occurs in response to doses ten times higher, i.e., 10–30 mg/kg in the liver and 30–100 mg/kg in the brain. Figure 2 also shows that at all MAO inhibitory dose levels, chlordimeform interferes more with the deamination of PEA than with that of the other substrates.

Essentially the same results were obtained after the oral administration of doses ranging from 1 to 300 mg/kg. A dose-related inhibitory effect of the substance on MAO-A was demonstrable in response to doses above 10 and 30 mg/kg in the liver and brain, respectively. In neither organ did the inhibition of MAO-A reach the 50% level, even at the already toxic dose of 300 mg/kg, but the threshold inhibitory dose of chlordimeform for type B-MAO was approximately 1 mg/kg. The ED_{50} values for PEA (substrate for MAO-B) and tyramine (mixed substrate) were determined by graphical interpolation (Table I) and proved to be very similar to those found after intraperi-

Table II. Effect of Chlordimeform (200 mg/kg p.o.) on the Contents of NA, DA, 5-HT, and 5-HIAA in the Rat Brain[d]

Pretreatment time, h	NA		DA		5-HT		5-HIAA	
	ng/g	%	ng/g	%	ng/g	%	ng/g	%
	340 ± 16	100	624 ± 31	100	330 ± 8	100	355 ± 17	100
1	360 ± 10	106	712 ± 19[a]	114	393 ± 13[b]	119	272 ± 14[b]	77
2	350 ± 3	103	788 ± 20[b]	126	400 ± 7[c]	121	258 ± 14[c]	73
4	408 ± 14[a]	120	760 ± 57	122	400 ± 13[c]	121	273 ± 22[a]	77
6	411 ± 20[a]	121	738 ± 43	118	386 ± 7[c]	117	266 ± 8[c]	75

[a] $p < 0.05$. [b] $p < 0.01$. [c] $p < 0.001$. [d] Figures quoted are $\bar{x} \pm S_{\bar{x}}$. $n = 5$ for NA and DA; $n = 8$ for 5-HT and 5-HIAA.

Table III. Effect of Chlordimeform (50 mg/kg i.p.) on the Accumulation of DOPA and 5-HTP in the Rat Brain after Inhibition of the Aromatic Amino Acid Decarboxylase with 3-Hydroxybenzylhydrazine Hydrochloride (NSD 1015)[c]

		Controls (NaCl 0.9% + NSD 1015)	Time (min) between chlordimeform and NSD 1015	
			0	90
Limbic forebrain	5-HTP	0.187 ± 0.009	0.158 ± 0.005[a]	0.154 ± 0.007[a]
	Trp	4.46 ± 0.14	4.58 ± 0.11	5.98 ± 0.26
Striatum	5-HTP	0.126 ± 0.007	0.081 ± 0.005[b]	0.070 ± 0.001[b]
	Trp	5.21 ± 0.19	5.02 ± 0.17	6.07 ± 0.32
Hemispheres	5-HTP	0.124 ± 0.003	0.084 ± 0.002[b]	0.064 ± 0.003[b]
	Trp	5.09 ± 0.03	5.17 ± 0.09	5.75 ± 0.03[a]
Limbic forebrain	L-DOPA	0.431 ± 0.019	0.418 ± 0.017	0.433 ± 0.011
	Tyr	13.8 ± 0.3	12.3 ± 0.2	14.1 ± 0.3
Striatum	L-DOPA	0.484 ± 0.025	0.493 ± 0.011	0.518 ± 0.020
	Tyr	13.4 ± 0.5	11.9 ± 0.4	13.21 ± 0.9
Hemispheres	L-DOPA	0.064 ± 0.003	0.062 ± 0.004	0.069 ± 0.004
	Tyr	12.7 ± 0.5	12.3 ± 0.7	14.1 ± 0.4

[a] $p < 0.05$. [b] $p < 0.01$. [c] Figures quoted are $\bar{x} \pm S_{\bar{x}}$ in μg/g, n = five extracts from two pooled regions each. The brains were removed for dissection 30 min after injection of NSD 1015 (100 mg/kg i.p.).

toneal treatment (Figure 2).

Effect on Biogenic Amines and Their Acidic Metabolites. In a pilot study, it was found that the 5-HT concentrations in the brain tissue from animals treated with chlordimeform in a dose of 100 mg/kg p.o. were considerably higher than in the controls, reaching a peak of 125% of the control values after 4 h and only returning to normal after 1–2 days; concomitantly, 5-HIAA in the brain was depressed to a slightly greater extent (data not shown). In order to determine the maximum effect, rats were treated with the sublethal dose of 200 mg/kg, p.o. Two experiments were carried out: in the first, the effect of chlordimeform on the endogenous contents of NA, DA, 5-HT, and 5-HIAA in the whole brain was monitored for 6 h after treatment, and in the second, its effect on the endogenous content of HVA and DOPAC in the striatum was followed up for 4 days.

The results of the first experiment are shown in Table II: NA content was increased by 20% but only after a latency period of at least 2 h. The DA and 5-HT concentrations were also 15–25% greater, but there were no marked differences between the values found 1 and 6 h after treatment. Similar changes were observed in the content of 5-HIAA. The concentration of the serotonin metabolite was lowered to the same extent (approximately 25%) from the first until the sixth hour after treatment.

In the second experiment, it was observed that after the administration of chlordimeform the concentration of DOPAC was altered to a greater extent than that of HVA. Two hours after treatment, DOPAC levels were reduced by more than 50%, whereas there was no change in the HVA levels. The only discernible effect of the compound on HVA was a comparatively small decrease in the concentration of this metabolite (approximately 30%) observed 1 day after treatment. By contrast, the reduction on the concentration of DOPAC was marked and persisted for more than 1 day (Figure 3).

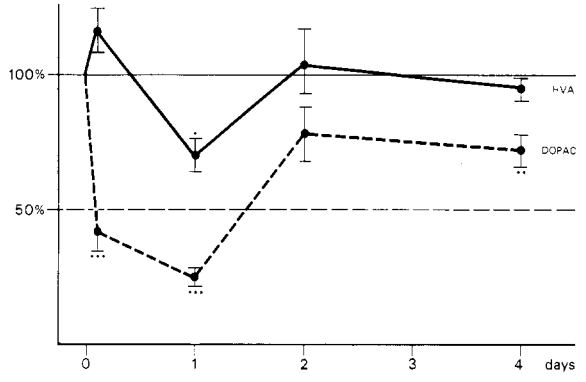

Figure 3. Time-course of the effect of chlordimeform (200 mg/kg, orally) on the concentrations of HVA and DOPAC in the rat corpus striatum. Each plotted value represents $\bar{x} \pm S_{\bar{x}}$ (n = 4 or 5) in percent of controls. The absolute control values were: HVA, 406 ± 30 ng/g; DOPAC, 797 ± 44 ng/g. (*) $p < 0.05$; (**) $p < 0.01$; (***) $p < 0.001$.

Effect on the Biosynthesis of Catecholamines and 5-HT. According to Carlsson et al. (1972), the accumulation of DOPA and 5-HTP after inhibition of the aromatic amino acid decarboxylase has been used as an index of the synthesis of catecholamines and 5-HT, respectively. Our own measurements of the concentrations of these amines and of tyrosine and tryptophan, their immediate precursors, demonstrate that chlordimeform diminished the accumulation of 5-HTP in the three brain regions studied

Table IV. Effect of Chlordimeform (50 mg/kg i.p.) on Monoamine Concentration in the Rat Brain after Inhibition of the Aromatic Amino Acid Decarboxylase with 3-Hydroxybenzylhydrazine Hydrochloride (NSD 1015)[b]

		Controls (NaCl 0.9% + NSD 1015)	Time (min) between chlordimeform and NSD 1015	
			0	90
Limbic forebrain	5-HT	0.229 ± 0.008	0.265 ± 0.008	0.284 ± 0.011[a]
	DA	0.965 ± 0.020	0.917 ± 0.063	1.061 ± 0.037
	NA	0.238 ± 0.007	0.264 ± 0.007	0.280 ± 0.009[a]
Striatum	5-HT	0.174 ± 0.003	0.160 ± 0.006	0.166 ± 0.005
	DA	2.713 ± 0.097	2.859 ± 0.138	2.652 ± 0.107
	NA	0.132 ± 0.004	0.128 ± 0.003	0.148 ± 0.007
Hemispheres	5-HT	0.150 ± 0.004	0.107 ± 0.005[a]	0.152 ± 0.003
	DA	0.016 ± 0.004	0.003 ± 0.002	0.016 ± 0.007
	NA	0.191 ± 0.001	0.200 ± 0.003	0.174 ± 0.004[a]

[a] $p < 0.01$. [b] Figures quoted are $\bar{x} \pm S_{\bar{x}}$ in μg/g, n = five extracts from two pooled regions each. The brains were removed for dissection 30 min after injection of NSD 1015 (100 mg/kg i.p.).

(Table III). In the striatum and in the hemispheres, this effect was slightly more pronounced 2 h after than 30 min after treatment. In the limbic forebrain, the effects observed at these times were identical.

There were no changes in tyrosine and tryptophan concentrations except a slight increase in the tryptophan concentration in hemispheres. In none of the three regions studied was any effect on the accumulation of DOPA detectable.

In these experiments (i.e., in the rats treated with NSD 1015), the concentrations of NA, DA, and 5-HT were also determined in the same three regions of the brain (Table IV). When chlordimeform was injected simultaneously with the administration of NSD 1015, 30% depletion of 5-HT was observed in the hemispheres without any changes in the other regions. The concentrations of NA and DA also were unaltered. In the pooled samples from animals killed 90 min after treatment with chlordimeform, small increases in 5-HT and NA were found in the limbic forebrain. In the other regions there was no notable change. The decrease in NA in the hemispheres was statistically significant but very small (<10%). In all regions the DA content remained unaltered.

DISCUSSION

The foregoing results clearly demonstrate that chlordimeform inhibits MAO activity in vivo, in the rat brain and liver. Consequently, the concentrations of deaminated metabolites of catecholamines and serotonin in the treated animals were reduced. The antienzymatic effect of chlordimeform observed in the present experiments merits some comment: In the first place, MAO is inhibited to a greater extent in the liver than in the brain. This might be related to the relatively greater affinity of chlordimeform to the liver than to the brain. Secondly, type B MAO, to use the nomenclature of Johnston (1968), is inhibited more than type A MAO. Thus in its effect on MAO, chlordimeform qualitatively resembles two well-known inhibitors: deprenyl, which, however, shows a greater preference for type B MAO, and pargyline, which in the lower dose range, i.e., up to approximately 3 mg/kg s.c. also inhibits MAO-B preferentially. (Squires, 1972; Maitre, 1976a,b). Thirdly, there is one important difference between chlordimeform on the one hand and deprenyl, pargyline, and other typical MAO inhibitors like tranylcypromine or iproniazid on the other, namely that chlordimeform-induced inhibition seems to be of competitive nature and fully reversible (Benezet and Knowles, 1976; Neumann and Voss, 1976). This is most probably the reason why MAO activity returns to normal relatively quickly after treatment with chlordimeform, e.g., in 1–2 days after i.p. injection of the high dose of 100 mg/kg; by contrast, after the classical MAO inhibitors normalization takes place much more slowly. Under the same conditions as in the experiments described here, a single injection of tranylcypromine (12 mg/kg s.c.) depressed MAO activity for more than 4 days, and iproniazid (100 mg/kg s.c.), deprenyl (10 mg/kg s.c.), and pargyline (50 mg/kg s.c.) induced an inhibition lasting approximately 3 weeks (Maitre et al., 1976). This is also the reason why no cumulative anti-MAO effect is produced by threshold doses of chlordimeform. In a separate study we injected chlordimeform intraperitoneally in a dose of 10 mg/kg either once or once daily for 4 days. Only tyramine and serotonin were used as substrates. MAO activity was inhibited to a marginal extent in the liver but not at all in the brain, and this effect was only observed when tyramine was used as substrate; there was no difference in the responses to single and repeated treatments (Maitre and Gfeller, 1975).

The effects of chlordimeform on catecholamine and serotonin metabolism in general confirm its MAO-inhibiting properties. However, in contrast to the pattern of increased monoamine concentrations followed by decreased monoamine synthesis produced by other MAO inhibitors (Carlsson et al., 1976), toxic doses of chlordimeform (200 mg/kg) had to be administered before any clear-cut increase in the concentration of catecholamines or 5-HT could be demonstrated. It appears that even a relatively high dose of 50 mg/kg did not reduce the capacity to deaminate catecholamines below the critical point at which catecholamine concentrations start to rise. Thus, end-product inhibition, which is known to be one of the principal regulatory factors in the synthesis of catecholamines, is of no importance at this dose of chlordimeform, which might perhaps explain the absence of any effect on DOPA accumulation.

The lack of effect of chlordimeform on the accumulation of DOPA may equally be related to its very weak HVA-depleting action. The typical inhibitors, pargyline, tranylcypromine, deprenyl, and iproniazid, decrease striatal HVA (Braestrup et al., 1975; Wilk et al., 1975; Maitre et al, 1976; Sharman, 1976) and not only DOPAC concentrations. The dissociation of the effect of chlordimeform on the two acidic DA metabolites may indicate that it exerts a preferential action on "intra-homoneuronal" DA metabolism (Sharman, 1976). It seems possible that the fairly selective inhibition of type B MAO may result in the accumulation of endogenous phenethylamine in the brain, as it has been shown to do after the administration of pargyline (Boulton et al., 1975). In view of the amphetamine-like properties of phenethylamine, it could be assumed that accumulation of this amine might lead to the release of dopamine from the intraneuronal storage sites.

This could explain the differential effect of chlordimeform on striatal HVA and DOPAC levels. In the case of amphetamine, the increase in HVA concentration and the concomitant decrease in DOPAC concentration have been clearly demonstrated (see Sharman, 1976).

5-HTP synthesis was reduced in all the areas of the brain examined and at both determination times after the administration of chlordimeform. Since 5-HTP synthesis was also decreased when chlordimeform was given simultaneously with NSD 1015, it is unlikely that unchanged 5-HTP caused a decrease in tryptophan hydroxylation, especially in view of earlier findings, indicating that no end-product feedback inhibition exists for tryptophan hydroxylase (Jequier et al., 1969). However, the diminution of 5-HTP accumulation may reflect a negative feedback, due to the increase in the amounts of serotonin available at the receptor sites, via 5-HT release, for instance.

It appears from these observations that chlordimeform differs in many respects from the typical MAO inhibitors. In several recent studies, it has been demonstrated convincingly that there is no causal relationship between the acaricidal and insecticidal or toxic action of chlordimeform and its MAO inhibitory effect. Up to now, these conclusions have been based on in vitro determinations of its antienzymatic activity. The present results were obtained in an in vivo–in vitro test system, i.e., after treatment of the rats with the compound. Comparison of these findings with the results obtained with classical MAO inhibitors fully corroborates the view that there is no causal relationship between anti-MAO and toxic effects. If chlordimeform is compared with iproniazid and pargyline, the two MAO inhibitors most often used as reference compounds, it is evident that the acute toxicity of all three drugs in the rat is of the same order of magnitude (Benson et al., 1952; Randall, 1958; Dittrich, 1966; Kenaga and End, 1974). Iproniazid and pargyline, however, are much more active MAO inhibitors. The results obtained when they were assayed under the same experimental conditions as chlordimeform have recently been published in part (Maitre, 1976b; Maitre et al., 1976). Iproniazid is 5–10 times more active and pargyline 10–100 times more active than chlordimeform in inhibiting type B MAO. For type A MAO the activity ratio of both these reference drugs in relation to chlordimeform is at least 100:1. In fact, it has never been possible to establish a positive correlation between MAO inhibitory activity and toxicity in experiments with many MAO inhibitors of various chemical structures (Felner and Waldmeier, unpublished results).

LITERATURE CITED

Abo-Khatwa, N., Hollingworth, R. M., *Life Sci.* 11, 1181 (1972).
Abo-Khatwa, N., Hollingworth, R. M., *Pestic. Biochem. Physiol.* 3, 358 (1973).
Andén, N.-E., Roos, B.-E., Werdinius, B., *Life Sci.* 2, 448 (1963).
Atack, C. V., Magnusson, T., *J. Pharm. Pharmacol.* 22, 625 (1970).
Atkinson, P. W., Binnington, K. C., Roulston, W. J., *J. Austral. Entomol. Sci.* 13, 207 (1974).
Aziz, S. A., Knowles, C. O., *Nature (London)* 242, 417 (1973).
Beeman, R. W., Matsumura, F., *Nature (London)* 242, 273 (1973).
Beeman, R. W., Matsumura, F., *Pestic. Biochem. Physiol.* 4, 325 (1974).
Benezet, H. J., Knowles, C. O., *Neuropharmacology* 15, 369 (1976).
Benson, W. M., Stefko, P. L., Roe, M. D., *Am. Rev. Tuberc.* 65, 376 (1952).
Boulton, A. A., Juorio, A. V., Philips, S. R., Wu, P. H., *Brain Res.* 96, 212 (1975).
Braestrup, C., Andersen, H., Randrup, A., *Eur. J. Pharmacol.* 34, 181 (1975).
Carlsson, A., Davis, J. N., Kehr, W., Lindqvist, M., Atack, C. V., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 275, 153 (1972).
Carlsson, A., Kehr, W., Lindqvist, M., *J. Neural Transm.* 39, 1 (1976).
Curzon, G., Green, A. R., *Br. J. Pharmacol.* 39, 653 (1970).
Dittrich, V., *J. Econ. Entomol.* 59, 889 (1966).
Felner, A., Waldmeier, P. C., Neurochemistry Laboratory Ciba-Geigy, on the tolerability of MAO inhibitors, unpublished results, 1975.
Holden, J. S., Hadfield, J. R., *Experientia* 31, 1015 (1975).
Jéquier, E., Robinson, D. S., Lovenberg, W., Sjoerdsma, A., *Biochem. Pharmacol.* 18, 1071 (1969).
Johnston, J. P., *Biochem. Pharmacol.* 17, 1285 (1968).
Kehr, W., Carlsson, A., Lindqvist, M., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 274, 273 (1972).
Kehr, W., Lindqvist, M., Carlsson, A., *J. Neural Transm.* 38, 173 (1976).
Kenaga, E. E., End, C. S., "Commercial and Experimental Organic Insecticides", special publication 74-1, Entomological Society of America, College Park, Maryland, 1974.
Knowles, C. O., Ahmad, S., Shrivastava, S. P., in "Pesticide Chemistry", Vol. 1, Tahori, A. S., Ed., Gordon and Breach, London, 1972, p 77.
Maitre, L., "Monoamine Oxidase and Its Inhibition", Ciba Foundation Symposium 39 (Elsevier, Excerpta Medica, North-Holland) Amsterdam, 1976a, p 25.
Maitre, L., "Monoamine Oxidase and Its Inhibition", Ciba Foundation Symposium 39 (Elsevier, Excerpta Medica, North-Holland) Amsterdam, 1976b, p 127.
Maitre, L., Delini-Stula, A., Waldmeier, P. C., "Monoamine Oxidase and Its Inhibition", Ciba Foundation Symposium 39 (Elsevier, Excerpta Medica, North-Holland) Amsterdam, 1976, p 247.
Maitre, L., Gfeller, W., test report submitted to the WHO, Geneva, 1975.
Murphy, G. F., Robinson, D., Sharman, D. F., *Br. J. Pharmacol.* 36, 107 (1969).
Neumann, R., Voss, G., *Experientia* 33, 23 (1977).
Randall, O. L., *J. Clin. Exp. Psychopathol.* 19 (Suppl. 1), 178 (1958).
Sharman, D. F., "Methods of Neurochemistry", Vol. 1, Fried, R., Ed., Dekker, New York, N.Y., 1971, p 83.
Sharman, D. F., "Monoamine Oxidase and Its Inhibition", Ciba Foundation Symposium 39 (Elsevier, Excerpta Medica, North-Holland) Amsterdam, 1976, p 203.
Squires, R. F., *Adv. Biochem. Psychopharmacol.* 5, 355 (1972).
Waldmeier, P., DeHerdt, P., Maitre, L., *Clin. Chem.* 20, 81 (1974).
Wilk, S., Watson, E., Travis, B., *Eur. J. Pharmacol.* 30, 228 (1975).
Wurtman, R. J., Axelrod, J., *Biochem. Pharmacol.* 12, 1439 (1963).

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