MOLECULAR PHARMACOLOGY, 11, 28-35

Some Structural Requirements for Inhibition of Type A and B Forms of Rabbit Monoamine Oxidase by Tricyclic Psychoactive Drugs

JEROME A. ROTH AND C. N. GILLIS

Departments of Anesthesiology and Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510

(Received July 17, 1974)

SUMMARY

ROTH, JEROME A. & GILLIS, C. N. (1975). Some structural requirements for inhibition of type A and B forms of rabbit monoamine oxidase by tricyclic psychoactive drugs. *Mol. Pharmacol.*, **11**, 28-35.

We have determined the ability of several structurally related tricyclic antidepressant and tranquilizing drugs to inhibit both the type A form of monoamine oxidase (measured by 5-hydroxytryptamine deamination) and the type B form of the enzyme [measured by β-phenylethylamine (PEA) deamination] of rabbit brain mitochondria. These studies indicate that both forms of the enzyme are inhibited by all tricyclic antidepressant drugs tested and that the B form of the oxidase is more susceptible to inhibition than the A form. Tricyclic drugs which have a double bond between the ring moiety and the aliphatic side chain were the most effective inhibitors of the B form of monoamine oxidase. Thus amitriptyline inhibited PEA deamination to the greatest extent, followed in decreasing order of effectiveness by chlorprothixene, imipramine, and chlorpromazine. Furthermore, chlorination in position 3 and hydroxylation in position 2 of imipramine and *N*-demethylation of amitriptyline did not alter the ability of the parent compound to inhibit the deamination of PEA. Chlorpromazine also inhibited PEA deamination, whereas the pharmacologically inactive tricyclic drug chlorpromazine sulfoxide failed to inhibit this oxidative reaction.

INTRODUCTION

Mitochondrial monoamine oxidase [monoamine:O_2 oxidoreductase (deaminating), EC 1.4.3.4] is a mixture of at least two different and distinguishable forms which possess different substrate and inhibitor specificities (1, 2). The type A or neuronal form of the enzyme, which deaminates 5-hydroxytryptamine, norepinephrine, and tyramine, is most sensitive to inhibition by harmine and clorgyline (3); the type B or extraneuronal form, which deaminates benzylamine, β-phenylethylamine, and tyramine, is inhibited selectively in some species by pargyline and Deprenyl (4). All these inhibitors, except harmine and related alkaloids, are covalently and irreversibly bound to the oxidase (5-7).

In a recent report from this laboratory

This investigation was supported by Public Health Service Grant 13315 from the National Heart and Lung Institute.

the tricyclic antidepressant drug imipramine was shown to inhibit reversibly the type A and B forms of rabbit brain and lung mitochondrial monoamine oxidase (8). The type B form of the oxidase was more susceptible to inhibition by imipramine than was the type A form; furthermore, the mono- and didesmethyl derivatives of imipramine inhibited the type B form of rabbit monoamine oxidase as effectively as the parent drug.

The ability of tricyclic psychoactive drugs, including imipramine, to inhibit flavoproteins such as monoamine oxidase is not unique. The antipsychotic drugs chlorpromazine and chlorprothixene have been shown previously to be effective inhibitors of D-amino acid oxidase (9) as well as mitochondrial monoamine oxidase (10–12). Chlorpromazine has also been found to inhibit succinic dehydrogenase (13). Therefore Gabay and Harris (9) suggested that the mechanism of action of tricyclic antipsychotic drugs was due to the ability to inhibit enzymes requiring as their prosthetic group flavin adenine dinucleotide. Although those authors investigated the structural requirements necessary for phenothiazine derivatives to inhibit D-amino acid oxidase, little is known about the structural features either of these drugs or of structurally related tricyclic antidepressant substances required for inhibition of mitochondrial monoamine oxidase. The purpose of this paper is to describe experiments designed to determine the structural features of tricyclic psychoactive drugs which promote inhibition of the type A and B forms of monoamine oxidase in rabbit mitochondria.

MATERIALS AND METHODS

Male albino rabbits weighing approximately 2 kg were used in all experiments. Preparation of brain mitochondria and the assay used to determine monoamine oxidase activity have been described previously (8). In brief, reaction mixtures containing either 1.8 μM ^{14}C-labeled β-phenylethylamine, 5-hydroxytryptamine, or tyramine were incubated with rabbit brain mitochondrial monoamine oxidase at 37° for different lengths of time. To this mixture were added varied amounts of tricyclic psychoactive drugs to be tested for their effect on type A or B monoamine oxidase. Reactions were terminated by the addition of either 2 ml of 0.4 M perchloric acid or 0.2 ml of 0.25 M $ZnSO_4$ and 0.2 ml of a saturated $Ba(OH)_2$ solution. The resulting precipitates were removed by centrifugation, and the [^{14}C]deaminated products formed were separated from the reaction mixtures by cation-exchange (Bio-Rex 70) chromatography. The radioactivity in the water effluents containing the deaminated products was measured in a liquid scintillation spectrometer (Packard Tri-Carb, model 3320).

[2-^{14}C]Tyramine HCl (42 mCi/mmole) and [2-^{14}C]5-hydroxytryptamine creatinine sulfate (58 mCi/mmole) were purchased from Amersham/Searle, and [2-^{14}C]β-phenylethylamine HCl (7 mCi/mmole) was obtained from New England Nuclear Corporation. Harmaline HCl was obtained from Aldrich Chemical Company. The structures and sources of the other tricyclic psychoactive drugs used in this study are shown in Table 1.

RESULTS

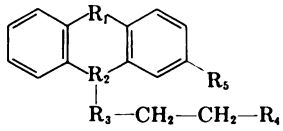
The effect of amitriptyline on the deamination of the mixed type A and B monoamine oxidase substrate tyramine is illustrated in Fig. 1. These results indicate that inhibition of tyramine deamination is biphasic, with an initial phase being inhibited 50% at approximately 2 μM amitriptyline and a second phase inhibited 50% around 100 μM amitriptyline. Although amitriptyline, like imipramine, inhibits both forms of the mitochondrial oxidase, this inhibitor is more selective for one of the two forms of the enzyme.

To ascertain which of the two forms of monoamine oxidase is more susceptible to inhibition by amitriptyline, studies were conducted using PEA[1] as a specific type B substrate and 5-HT as a specific type A substrate. Results of these experiments (Fig. 2) indicate that PEA deamination is inhibited at lower concentrations of ami-

[1] The abbreviations used are: PEA, β-phenylethylamine; 5-HT, 5-hydroxytryptamine.

TABLE 1

Structures of tricyclic psychoactive drugs



Name	R_1	R_2-R_3	R_4	R_5	Source
Imipramine[a]	CH_2—CH_2	N—CH_2	$N(CH_3)_2$	H	Ciba-Geigy
Chlorimipramine[a]	CH_2—CH_2	N—CH_2	$N(CH_3)_2$	Cl	Ciba-Geigy
2-Hydroxydesmethylimipramine[b]	CH_2—CH_2	N—CH_2	$NH(CH_3)$	H	Ciba-Geigy
Iminodibenzyl[c]	CH_2—CH_2	N—H		H	Aldrich
Amitriptyline[a]	CH_2—CH_2	C=CH	$N(CH_3)_2$	H	Merck Sharp & Dohme
Nortriptyline[a]	CH_2—CH_2	C=CH	$NH(CH_3)$	H	Eli Lilly
Protriptyline[a]	CH=CH	$CH=CH_2$	$NH(CH_3)$	H	Merck Sharp & Dohme
Cyclobenzaprine[a]	CH=CH	C=CH	$N(CH_3)_2$	H	Hoffmann-La Roche
Chlorpromazine[a]	S	N—CH_2	$N(CH_3)_2$	Cl	Smith Kline & French
Chlorpromazine sulfoxide[a]	S—O	N—CH_2	$N(CH_3)_2$	Cl	Regis Chemical Company
Chlorprothixene[c]	S	C=CH	$N(CH_3)_2$	Cl	Hoffmann-La Roche

[a] HCl salt.
[b] Fumarate salt.
[c] Free base.

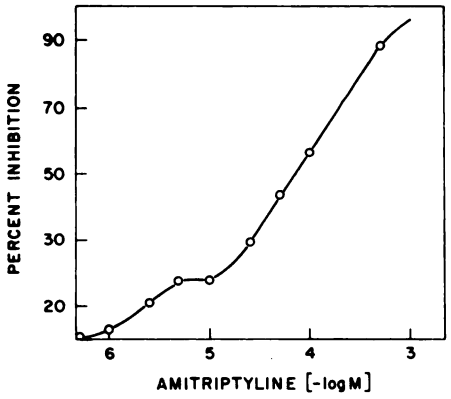


FIG. 1. *Effect of amitriptyline on deamination of tyramine*

Reaction mixtures containing 3.6 nmoles of [^{14}C]tyramine, 0.45 mg of protein, and varying amounts of amitriptyline in a total of 2 ml of 0.05 M potassium phosphate buffer, pH 7.4, were incubated at 37° for 30 min. In the absence of amitriptyline 0.68 nmole of deaminated product was formed.

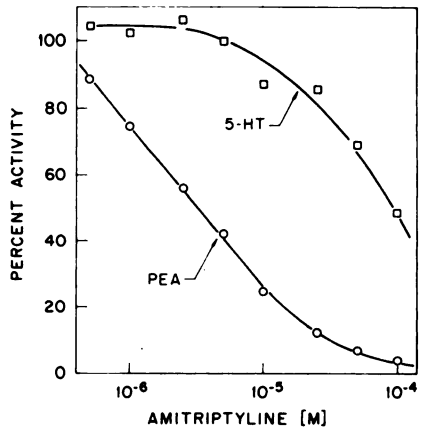


FIG. 2. *Effect of amitriptyline on deamination of phenylethylamine and 5-hydroxytryptamine*

Reaction mixtures containing 3.6 nmoles of [^{14}C]PEA or [^{14}C]5-HT, 0.45 mg of protein, and varying amounts of amitriptyline in a total of 2 ml of 0.05 M potassium phosphate buffer, pH 7.4, were incubated at 37° for 8 or 40 min, respectively. In the absence of amitriptyline, 1.94 and 0.38 nmoles of the deaminated products of PEA and 5-HT, respectively, were formed.

triptyline than that of 5-HT. Under the conditions used approximately 50% inhibition of PEA and 5-HT deamination is achieved at drug concentrations of 3 and 90 μM, respectively. Thus inhibition of the type A form of monoamine oxidase requires around 30 times more amitriptyline than is required to inhibit the type B form of the oxidase.

A comparison of several drugs structurally related to amitriptyline with respect to their ability to inhibit deamination of PEA is illustrated in Fig. 3. Both amitriptyline and chlorprothixene are considerably more effective inhibitors of PEA deamination

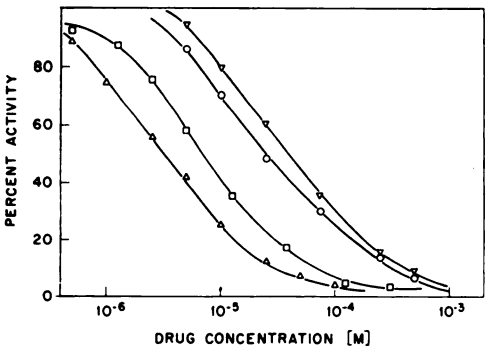


FIG. 3. *Effect of structurally related tricyclic drugs on phenylethylamine deamination*

Reaction mixtures containing 3.6 nmoles of [^{14}C]PEA, varying amounts of mitochondrial protein (0.43–0.75 mg), and amitriptyline (Δ——Δ), chlorprothixene (□——□), imipramine (○——○), or chlorpromazine (▽——▽) in a total of 2 ml of 0.05 M potassium phosphate buffer, pH 7.4, were incubated at 37° for 5–10 min.

than either imipramine or chlorpromazine. Thus 50% inhibition of PEA deamination was produced by 3 μM amitriptyline, 7 μM chlorprothixene, 25 μM imipramine, and 40 μM chlorpromazine. In contrast, when 5-HT is used as substrate (Fig. 4), the abilities of these drugs, with the exception of chlorpromazine, to inhibit deamination of 5-HT are very similar. Approximately 20% inhibition of 5-HT deamination is observed at drug concentrations of 30 μM, and 90% inhibition is achieved at drug concentrations around 400 μM. The ability of chlorpromazine to inhibit 5-HT deamination is considerably more variable than that of the other drugs tested. Since percentage inhibition may not accurately reflect the binding affinities of these drugs for the different forms of monoamine oxidase K_i was also determined from Dixon and Lineweaver-Burk plots. These data (Table 2) clearly indicate that these drugs possess greater affinity for the B form of the oxidase than for the A form, and thus correspond with the results for percentage inhibition of PEA and 5-HT deamination shown in Figs. 3 and 4. The nature of amitriptyline and chlorprothixene binding to the B form of the oxidase was also examined, and these results are illustrated by the Lineweaver-Burk plots shown in Fig. 5. Amitriptyline displays a mixed type of inhibition, and thus inhibits the oxidase in a manner similar to that previously shown for imipramine (8). On the other hand, chlorprothixene inhibits PEA deamination competitively.

In order to determine the structural features of amitriptyline and chlorprothixene which enhance their ability to inhibit PEA deamination (Fig. 3), several structurally related derivatives of these drugs, which varied in positions R_1, R_2, and R_3 (see Table 1), were examined. As shown in Table 3, protriptyline, an antidepressant drug which possesses a double bond in position R_1 (Table 1) and a completely saturated side chain, is less effective than amitriptyline in inhibiting PEA deamination, whereas the psychoactive drug cyclobenzaprine, which contains a double

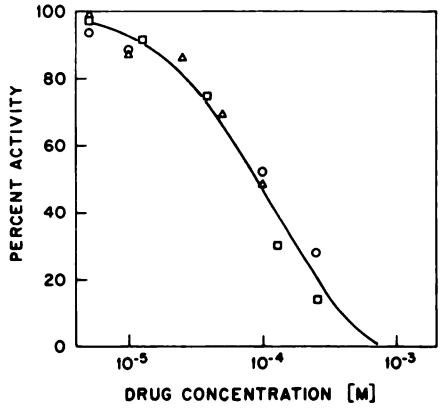


FIG. 4. *Effects of structurally related tricyclic drugs on 5-hydroxytryptamine deamination*

Reaction mixtures containing 3.6 nmoles of [^{14}C]5-HT, varying amounts of mitochondrial protein (0.45–0.85 mg), and amitriptyline (Δ——Δ), chlorprothixene (□——□), or imipramine (○——○), in a total of 2 ml of 0.05 M potassium phosphate buffer, pH 7.4, were incubated at 37° for 15–40 min.

TABLE 2

Binding constants for several tricyclic psychoactive drugs to type A and B monoamine oxidase

Inhibitor	K_i	
	Type A	Type B
	M	*M*
Imipramine	3×10^{-4}	4×10^{-5}
Amitriptyline	2×10^{-4}	5×10^{-6}
Chlorprothixene	8×10^{-5}	6×10^{-6}

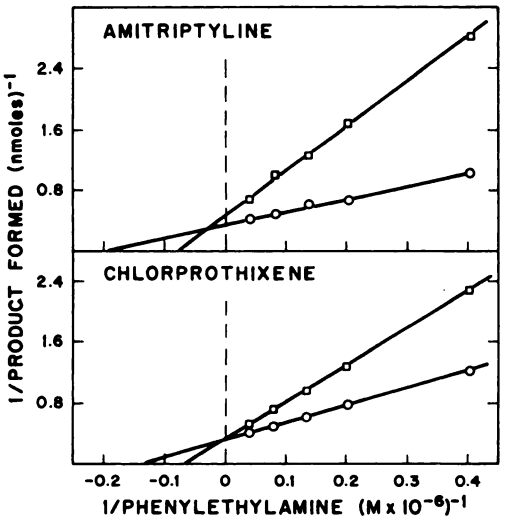


FIG. 5. *Lineweaver-Burk plot for inhibition of phenylethylamine deamination by amitriptyline and chlorprothixene*

Varying amounts of [^{14}C]PEA were incubated in the absence (O——O) or presence (□——□) of 5 μM amitriptyline or chlorprothixene at 37° for 10 min. Protein concentration was 0.18 mg/2 ml of reaction mixture.

bond in position R_1 and R_2–R_3, inhibits this reaction only slightly less than that of amitriptyline.

The reduced ability of protriptyline (Table 2), in comparison with amitriptyline, to inhibit PEA deamination could be caused either by the double bond in the cyloheptene ring (position R_1), by lack of the double bond in position R_2–R_3, or by lack of an *N*-methyl group in position R_4. The observation that cyclobenzaprine and nortriptyline are more effective inhibitors of PEA deamination than protriptyline (Table 3) suggests that the lack of the double bond in position R_2–R_3 or protriptyline and in imipramine and chlorpromazine decreases the ability of these drugs to inhibit the type B form of rabbit monoamine oxidase. Thus it is the double bond leading to the side chain of amitriptyline, nortriptyline, chlorprothixene, and cyclobenzaprine which facilitates the interaction of these drugs with the B form of the enzyme.

The antipsychotic drugs examined, chlorpromazine and chlorprothixene, contain chlorine in position R_5, whereas all the antidepressant drugs tested lack this substituent. Accordingly, the effect of the chlorine atom in position R_5 on the ability of imipramine to inhibit PEA deamination was also measured. The results (Table 4) indicate that chlorine substitution in R_5 of the iminodibenzyl moiety of imipramine does not alter the inhibitory properties of the parent antidepressant drug. Also examined for its ability to inhibit PEA deamination was the naturally occurring antidepressant metabolite of imipramine, 2-hydroxydesmethylimipramine. As shown in Table 4, this metabolite was also an effective inhibitor of the type B form of mitochondrial monoamine oxidase.

Also examined for their ability to inhibit PEA deamination were the naturally occurring mixed-function oxidase metabolites of chlorpromazine, 7-hydroxychlorpromazine and chlorpromazine sulfoxide. The results (Table 5) indicate that the psychoactive 7-hydroxy derivative of chlorpromazine inhibits PEA deamination whereas the pharmacologically inactive metabolite, chlorpromazine sulfoxide, does not inhibit this reaction. Also presented in Table 5 are the effects of iminodibenzyl and org GB 94, a new tetracyclic an-

TABLE 3

Effects of dibenzocycloheptene psychoactive drugs on phenylethylamine deamination

Reaction mixtures contained 3.6 nmoles of PEA, tricyclic psychoactive drug, and 0.38–0.45 mg of protein in a total of 2 ml of buffer. The means ± standard deviations for percentage inhibition for experiments 1 and 2 are based on three and four separate determinations, respectively.

Inhibitor	Inhibitor concentration	Inhibition
	M	%
Experiment 1		
Amitriptyline	5.0×10^{-5}	89.7 ± 0.9
Nortriptyline	5.0×10^{-5}	84.9 ± 0.4
Protriptyline	5.0×10^{-5}	59.3 ± 1.0
Experiment 2		
Amitriptyline	1.0×10^{-5}	74.4 ± 2.7
Nortriptyline	1.0×10^{-5}	62.4 ± 4.5
Protriptyline	1.0×10^{-5}	28.0 ± 4.1
Cyclobenzaprine	1.0×10^{-5}	58.8 ± 1.9

TABLE 4

Effects of iminodibenzyl antidepressant derivatives on phenylethylamine deamination

Reaction mixtures contained 3.6 nmoles of PEA or 5-HT, 0.38 mg of protein, and 0.1 μmole of the iminodibenzyl derivative in a total of 2 ml of buffer. Average values for product formed are based on experiments run in duplicate.

Inhibitor	Deaminated product formed		Inhibition
	Expt. 1	Expt. 2	
			%
None	0.436	0.185	
Imipramine	0.137	0.061	67.9 ± 1.3
Chlorimipramine	0.172	0.068	61.9 ± 2.3
2-Hydroxydesmethyl-imipramine	0.180		58.7 ± 2.4

TABLE 5

Effects of psychoactive drugs on phenylethylamine deamination

Reaction mixture contained 3.6 nmoles of PEA, 0.36 mg of protein, and varying amounts of the psychoactive drugs in a total of 2 ml of buffer, and were incubated at 37° for 5 min.

Inhibitor	Inhibitor concentration	Inhibition
	M	%
Chlorpromazine	5×10^{-5}	45.6 ± 2.7
Chlorpromazine	1×10^{-4}	61.0 ± 5.3
7-Hydroxychlorpromazine	5×10^{-5}	40.1
Chlorpromazine sulfoxide	5×10^{-5}	<1
Iminodibenzyl	1×10^{-4}	49.9 ± 5.8
Org GB 94	1×10^{-4}	78.7 ± 3.5

tidepressant drug, on PEA deamination. At a drug concentration of 100 μM, org GB 94 inhibits this reaction almost 80%, whereas the parent compound of imipramine, iminodibenzyl, inhibits PEA deamination aroung 50%.

DISCUSSION

The tricyclic psychoactive drugs examined in this study can be divided into two general classes, based on their ability to inhibit the deamination of PEA by type B monoamine oxidase. The first class, including amitriptyline, nortriptyline, chlorprothixene, and cyclobenzaprine, inhibits this reaction 50% at approximately 5 μM. The second class of compounds, including imipramine, several imipramine analogues, protriptyline, and chlorpromazine, inhibits PEA deamination approximately 50% at drug concentration of 30 μM. From the results presented in this paper it can be seen that differences in the abilities of these drugs to inhibit the type B form of rabbit monoamine oxidase can be attributed to the presence of the double bond in the side chain (position R_2–R_3). In this regard it is interesting that Taylor *et al.* (14) found removal of the ethylenic moiety from styrylquinolinium derivatives to reduce their ability to inhibit dopamine deamination. They suggested that the double bond may enhance the ability of these compounds to inhibit monoamine oxidase by promoting production of a charge-transfer complex with the FAD prosthetic group of the oxidase. Belleau and Moran (15) previously suggested that the double bond (sp^2) character of the α and β carbon atoms in the cyclopropane ring of tranylcypromine, a monoamine oxidase inhibitor, may also promote formation of a charge-transfer complex with the flavin cofactor of the enzyme. Thus the double bond in the side chain of the tricyclic psychoactive drugs examined may similarly facilitate formation of a charge-transfer complex with the isoalloxazine moiety of FAD of the type B form of rabbit monoamine oxidase.

The extent to which a charge-transfer complex may contribute to the inhibitory action of the tricyclic drugs used in these studies is not known. It has been demonstrated that flavins are capable of forming charge-transfer complexes with a wide variety of polycyclic aromatic substances (16–19). Belleau and Moran (15) speculated that the harmine alkaloids, potent inhibitors of monoamine oxidase, may also form a charge-transfer complex with the flavin moiety of the enzyme. The ring structures of these alkaloids are not very different from those of the psychoactive agents used in this study. It has been shown by Karreman *et al.* (20) and Yagi and Ozawa (21) that chlorpromazine does indeed form charge-transfer complexes

with riboflavin and FAD, respectively. In this regard, molecular orbital calculations have indicated that chlorpromazine is an extremely good electron donor (22). Borg and Cotzias (23) showed that chlorpromazine in the presence of trace elements such as manganese can readily lose an electron and produce the free radical cation. Imipramine was also shown by Borg (24) to form a free radical under similar conditions. However, chlorpromazine sulfoxide, a phenothiazine derivative which does not inhibit monoamine oxidase (see Table 5), also does not produce the cationic chromophore (25). These data suggest that it may be the electron-donating properties of the tricyclic moieties of these drugs which influence their ability to inhibit flavoproteins such as monoamine oxidase.

Roth and McCormick (26) have shown that the ability of purine ribonucleoside derivatives to form an intermolecular complex with riboflavin is decreased by the presence of chlorine in position 6 of the nucleoside. In contrast with these observations, Gabay and Harris (9) found that chlorine substitution in position R_5 of the phenothiazine drugs is essential for inhibition of D-amino acid oxidase. In contrast, our results indicate that chlorine does not influence the ability of imipramine to inhibit PEA deamination. Likewise, the presence of a 2-hydroxy group on the iminodibenzyl moiety of imipramine does not alter the ability of this antidepressant drug to inhibit the reaction. Moreover, as previously shown for imipramine (8), the *N*-demethylated mixed-function oxidase product of amitriptyline is an effective inhibitor of the type B form of rabbit monoamine oxidase. Therefore it may be concluded that the side chain of the tricyclic drugs is not essential for inhibition of monoamine oxidase. This conclusion is clearly substantiated by the data in Table 5, which show that iminodibenzyl, i.e., imipramine without the side chain, also inhibits PEA deamination.

It is interesting that all tricyclic antidepressant drugs tested in this laboratory inhibit the B form of rabbit monoamine oxidase to a greater extent than the A form. It can also be seen that many of the other known monoamine oxidase inhibitors [tranylcypromine (27), Deprenyl (4), and pargyline (4)] that were or are being presently used or tested clinically as antidepressant agents also inhibit the B form of the oxidase to the greatest extent. Whether these observations are simply fortuitous or whether they represent a property that is necessary for the clinical action of antidepressant drugs remains to be determined. It is therefore interesting to find (see Table 5) that the new antidepressant tetracyclic compound org GB 94 (28, 29) also inhibits PEA deamination. Although not indicated, org GB 94 also is a less effective inhibitor of the A form of the oxidase. These properties of org GB 94 become even more significant in view of the finding that this compound, unlike the tricyclic antidepressant drugs, does not effectively prevent the reuptake of 5-HT in rat brain cortical slices (30).

The relationship between the ability of the tricyclic psychoactive drugs to inhibit rabbit mitochondrial type A or B monoamine oxidase and the clinical effects of these drugs in man is not apparent from the results obtained in this study. Chlorpromazine and imipramine are equipotent inhibitors of the type B form of rabbit monoamine oxidase, although these drugs reportedly have opposite clinical effects (31). Although the clinical indications for use of these drugs lie at opposite ends of the spectrum, it has been demonstrated that pharmacological and biochemical properties of these psychoactive agents are qualitatively similar (32–36). In addition, both drugs have been shown to have analeptic and depressant activities *in vivo* (37, 38). The distinction between inhibitory and therapeutic properties of the antidepressant drug amitriptyline and the antipsychotic drug chlorprothixene, however, is not as clear as in the above case. Chlorprothixene, although primarily used as an antipsychotic agent, has also been reported to have some antidepressant characteristics (39–41).

Extrapolation of the data presented in this paper to human type A and B monoamine oxidase is difficult. In this regard Squires (3) has reported that Deprenyl

exerts very little selective inhibition on the type B fraction of rabbit monoamine oxidase but is extremely selective for the type B form of the human enzyme. Accordingly, a thorough investigation on the effects of tricyclic psychoactive drugs on preparations of human type A and B monoamine oxidase is needed before the significance of this inhibitory action can be related to clinical mode of action.

ACKNOWLEDGMENTS

We wish to thank the drug companies listed in Table 1 for providing samples of the compounds tested. We are grateful to Dr. R. Roth and Dr. B. S. Bunney for kindly supplying us with chlorimipramine, 7-hydroxychlorpromazine, and chlorpromazine sulfoxide, and to Dr. S. Gabay (Biochemical Research Laboratory, Veterans Administration Hospital, Brockton, Mass.) for sending us org GB 94.

REFERENCES

1. Johnston, J. P. (1968) *Biochem. Pharmacol.*, **17**, 1285-1297.
2. McCauley, R. & Racker, E. (1973) *Mol. Cell. Biochem.*, **1**, 73-81.
3. Squires, R. F. (1972) *Adv. Biochem. Psychopharmacol.*, **5**, 355-370.
4. Yang, H.-Y. T. & Neff, N. H. (1973) *J. Pharmacol. Exp. Ther.*, **187**, 365-371.
5. Hellerman, L. & Erwin, V. G. (1968) *J. Biol. Chem.*, **243**, 5234-5243.
6. Knoll, J., Ecseri, Z., Kelemen, K., Nievel, J. & Knoll, B. (1965) *Arch. Int. Pharmacodyn. Ther.*, **155**, 154-164.
7. Udenfriend, S., Witkop, B., Redfield, B. G. & Weissbach, H. (1958) *Biochem. Pharmacol.*, **1**, 160-165.
8. Roth, J. A. & Gillis, C. N. (1974) *Biochem. Pharmacol.*, **23**, 2537-2545.
9. Gabay, S. & Harris, S. R. (1967) *Biochem. Pharmacol.*, **16**, 803-812.
10. Tipton, K. F. (1968) *Biochim. Biophys. Acta*, **159**, 451-459.
11. Fischer, A. G., Schulz, A. R. & Oliner, L. (1968) *Biochim. Biophys. Acta.*, **159**, 460-471.
12. Yasunobu, K. T. & Oi, S. (1972) *Adv. Biochem. Psychopharmacol.*, **5**, 91-105.
13. Karokawa, M., Naruse, H., Kato, M. & Yabe, T. (1957) *Folia Psychiatr. Neurol. Jap.*, **10**, 354-363.
14. Taylor, R. J., Markley, E. & Ellenbogen, L. (1967) *Biochem. Pharmacol.*, **16**, 79-86.
15. Belleau, B. & Moran, J. (1963) *Ann. N. Y. Acad. Sci.*, **107**, 822-839.
16. Weber, G. (1950) *Biochem. J.*, **47**, 114-121.
17. Harbury, H. A. & Foley, K. A. (1958) *Proc. Natl. Acad. Sci. U. S. A.*, **44**, 662-668.
18. Harbury, H. A., La Noue, K. F., Loach, P. A. & Amick, R. M. (1959) *Proc. Natl. Acad. Sci. U. S. A.*, **45**, 1708-1717.
19. Wright, L. D. & McCormick, D. B. (1964) *Experientia*, **20**, 501-506.
20. Karreman, G., Isenberg, I. & Szent-Györgyi, A. (1959) *Science*, **130**, 1191-1192.
21. Yagi, K. & Ozawa, T. (1959) *Nature*, **184**, 982-983.
22. Orloff, M. K. & Fitts, D. D. (1961) *Biochim. Biophys. Acta*, **47**, 596-599.
23. Borg, D. C. & Cotzias, G. C. (1962) *Proc. Natl. Acad. Sci. U. S. A.*, **48**, 623-642.
24. Borg, D. C. (1965) *Biochem. Pharmacol.*, **14**, 115-120.
25. Borg, D. C. & Cotzias, G. C. (1962) *Proc. Natl. Acad. Sci. U. S. A.*, **48**, 617-623.
26. Roth, J. A. & McCormick, D. B. (1967) *Photochem. Photobiol.*, **6**, 657-664.
27. Fuller, R. W. (1972) *Adv. Biochem. Psychopharmacol.*, **5**, 339-354.
28. Quantock, D., Fell, P. & Vander Berg, W. (1973) *Eur. J. Clin. Pharmacol.*, **5**, 166-173.
29. Itil, T. M., Polvan, N. & Hsu, W. (1972) *Curr. Ther. Res. Clin. Exp.*, **14**, 395-413.
30. Kafoe, W. F. & Leonard, B. E. (1973) *Arch. Int. Pharmacodyn. Ther.*, **206**, 389-391.
31. Klerman, G. L. & Cole, J. O. (1965) *Pharmacol. Rev.*, **17**, 101-141.
32. Abadom, P. N., Ahmed, K. & Scholefield, P. G. (1961) *Can. J. Biochem.*, **39**, 551-558.
33. Bartholini, G., Pletscher, A. & Gey, K. F. (1961) *Experientia*, **17**, 541-542.
34. Loutrup, S. (1963) *J. Neurochem.*, **10**, 471-477.
35. Carver, M. J. (1963) *Biochem. Pharmacol.*, **12**, 19-24.
36. Sulser, F. & Dingell, J. V. (1967) *Biochem. Pharmacol.*, **17**, 634-636.
37. Herr, F., Stewart, J. & Chares, M.-P. (1961) *Arch. Int. Pharmacodyn Ther.*, **134**, 328-342.
38. Lapin, I. P. (1962) *Psychopharmacologia*, **3**, 413-422.
39. Kruse, W. (1960) *Am. J. Psychiatr.*, **116**, 849-850.
40. Cornu, F. & Hoffet, H. (1961) *Dis. Nerv. Syst.*, **22**, 40-44.
41. Darling, H. F. (1961) *Dis. Nerv. Syst.*, **22**, 154-156.