Biochemical Pharmacology, Vol. 32, No. 7, pp. 1243–1249, 1983.
Printed in Great Britain.

0006-2952/83/071243-07 $03.00/0

N-[2-(*o*-IODOPHENOXY)ETHYL]CYCLOPROPYLAMINE HYDROCHLORIDE (LY121768), A POTENT AND SELECTIVE IRREVERSIBLE INHIBITOR OF TYPE A MONOAMINE OXIDASE

RAY W. FULLER,* SUSAN K. HEMRICK-LUECKE and BRYAN B. MOLLOY
Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, IN 46285, U.S.A.

(*Received* 15 *July* 1982; *accepted* 23 *September* 1982)

Abstract—The effects of *N*-[2-(*o*-iodophenoxy)ethyl]cyclopropylamine hydrochloride (LY121768) on types A and B monoamine oxidase (MAO) assayed with radiocarbon-labeled serotonin and phenylethylamine, respectively, were studied *in vitro* and *in vivo*. Type A MAO from rat brain was inhibited *in vitro* by LY121768 with an IC_{50} of 4×10^{-10} M, whereas 2500 times higher concentrations of LY121768 ($IC_{50} = 1 \times 10^{-6}$ M) were required to inhibit type B MAO. The inhibition of type A MAO increased with time of incubation of LY121768 with enzyme prior to substrate addition and persisted after dialysis, indicative of irreversible inhibition. The irreversible inactivation was prevented by harmaline, a reversible, competitive inhibitor of type A MAO, indicating a requirement for catalytic activity of MAO in the time-dependent inactivation by LY121768. In rats, LY121768 selectively inhibited type A MAO in brain and in liver at low doses. The inhibition of type A MAO persisted for several days after a single 10 mg/kg i.p. dose of LY121768 and was associated with a significant increase in brain dopamine, norepinephrine and epinephrine concentrations and a significant decrease in the concentration of the dopamine metabolites, homovanillic acid and 3,4-dihydroxyphenylacetic acid. The inactivation of type A MAO by LY121768 *in vivo* was prevented by co-administration of harmaline, indicating a similar mechanism for the *in vivo* inactivation as for the *in vitro* inactivation of MAO by LY121768. A reasonable inference from these data and from previous literature is that LY121768 acts as a "suicide substrate" for MAO and inactivates the enzyme by formation of a reactive intermediate which binds covalently to the enzyme. The presence of iodine in the LY121768 molecule not only confers high selectivity for type A MAO but offers a site for radionuclide introduction that might be a useful means of labeling type A MAO *in vitro* or *in vivo* for various purposes.

Monoamine oxidase [MAO; monoamine:oxygen oxidoreductase (deaminating), EC 1.4.3.4] catalyzes the oxidative deamination of numerous biogenic amines, including serotonin, dopamine, norepinephrine and epinephrine. MAO is present in brain and in peripheral sympathetically innervated tissues, although its localization is not limited to neurons in any of these tissues. Inhibitors of MAO are used clinically in the treatment of mental depression and hypertension. In addition, MAO inhibitors have been useful pharmacologic tools in clinical and preclinical studies for exploring roles of specific amine neurotransmitters in various physiologic functions.

Multiple forms of MAO are known to exist, and the concept of type A and type B MAO as distinct entities with differing specificities for substrates and inhibitors has been useful in considering physiologic roles of MAO and pharmacologic consequences of inhibiting it [1, 2]. Simply stated, serotonin is a preferred substrate and clorgyline, harmaline and LY51641 are selective inhibitors of type A MAO. Phenylethylamine and benzylamine are preferred substrates for type B MAO, which is inhibited with reasonably high selectivity by deprenyl and with lesser selectivity by pargyline [1]. These descriptions of types A and B MAO represent oversimplifications, since the enzymes in some tissues do not have all of the characteristics of one of these single types of MAO [2]. Nevertheless, consideration of substrates and inhibitors within this conceptual framework can be useful if one is aware of the limitations implicit therein.

Numerous potent, irreversible inhibitors of MAO have been described, all of which probably act through a k_{cat} mechanism, being acted on by MAO to form a reactive intermediate species that combines with a functional group on the apoprotein or cofactor moiety of the enzyme leading to irreversible inactivation. Although some of these inhibitors are nonselective in affecting both type A and type B MAO, others are selective for either type A or type B MAO. The first highly selective irreversible inhibitor of type A MAO to be described in the literature was LY51641, *N*-[2-(*o*-chlorophenoxy)ethyl]cyclopropylamine hydrochloride [3], and the characteristics of this inhibitor [4] and others within its chemical series [5] have been described in detail. A compound in the series not synthesized until recently contains an iodine in place of the chloro substitution in LY51641. This compound, LY121768 (see Fig. 1), is of interest because the iodine substituent not only confers high selectivity for type A MAO but also offers a site for introduction of a radionuclide that could permit irreversible labeling of type A MAO. Some characteristics of LY121768 as an inhibitor of MAO *in vitro* and *in vivo* are described in this paper.

* Author to whom correspondence should be addressed.

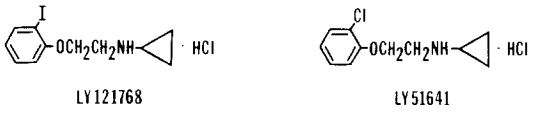

Fig. 1. Structures of LY121768 and LY51641.

MATERIALS AND METHODS

Male Wistar rats weighing about 150 g were purchased from Harlan Industries, Cumberland, IN, and were housed in groups of five with food and water freely available. LY121768 and LY51641 were synthesized in the Lilly Research Laboratories, and harmaline hydrochloride was purchased from the Sigma Chemical Co., St. Louis, MO. The substrates used to assay types A and B MAO, respectively, were 100 μM [2-^{14}C]5-hydroxytryptamine binoxalate and 12.5 μM [1-^{14}C]phenylethylamine hydrochloride, purchased from the New England Nuclear Corp. (Boston, MA). The radiometric assay was modified from the method of Wurtman and Axelrod [6] as described previously [7]. For *in vitro* studies, mitochondria isolated from rat liver or brain were ultrasonicated in suspension for 5 min in short bursts in a Bronwill Biosonik III. After centrifugation at 100,000 *g* for 30 min, the supernatant fluid was removed, stored frozen in small aliquots, and used as the source of MAO.

For *in vivo* studies, rats were given i.p. injections of aqueous solutions of the drugs and were killed by decapitation at the time intervals specified. Tissues were quickly removed and frozen on dry ice. MAO activity in whole homogenates was assayed as described above. Catecholamines and their metabolites were measured by high performance liquid chromatography with electrochemical detection [8, 9]. All *in vivo* data are shown as mean values ± standard errors for five rats per group. Statistical comparisons were made by Student's *t*-test.

RESULTS

In vitro *studies*. Figure 2 shows the concentration dependence of the inhibition of type A MAO (serotonin as substrate) and of type B MAO (phenylethylamine as substrate) from rat brain by LY51641 and by LY121768. The iodo compound was three times as potent as the chloro compound as an inhibitor of serotonin oxidation. The two compounds were similar in potency in inhibiting phenylethylamine oxidation, though the iodo compound was slightly less potent than the chloro compound. LY121768 was 2500 times more potent as an inhibitor of type A MAO than of type B MAO, whereas LY51641 was only about 600 times more potent against type A compared to type B MAO. Thus, the already high selectivity of LY51641 is enhanced by replacement of the chloro with an iodo substituent.

For studies of the mechanism of type A MAO inhibition by LY121768, MAO from rat liver mitochondria was used because of the higher enzymatic activity of this preparation and the consequent ease with which dilution experiments after preincubation of enzyme with inhibitor could be done. The data in Fig. 3 show that the inhibition of type A MAO from liver *in vitro* by LY121768 was time dependent. Less than 60% inhibition of MAO activity occurred when 10^{-9} M LY121768 was added to MAO simultaneously with the substrate (100 μM serotonin) (Fig. 3a). When that same concentration of LY121768 was added prior to the substrate, greater inhibition was produced. The percent inhibition increased with time to a maximum of just over 80% inhibition after 6 min. Figure 3b shows that a linear relationship was obtained when percentage of MAO activity remaining was plotted on a logarithmic scale against time of preincubation at very short preincubation times. In these experiments the enzyme and inhibitor mixtures were diluted 15-fold following preincubation, so higher concentrations of inhibitor were used. The linear rate of inactivation of enzyme was concentra-

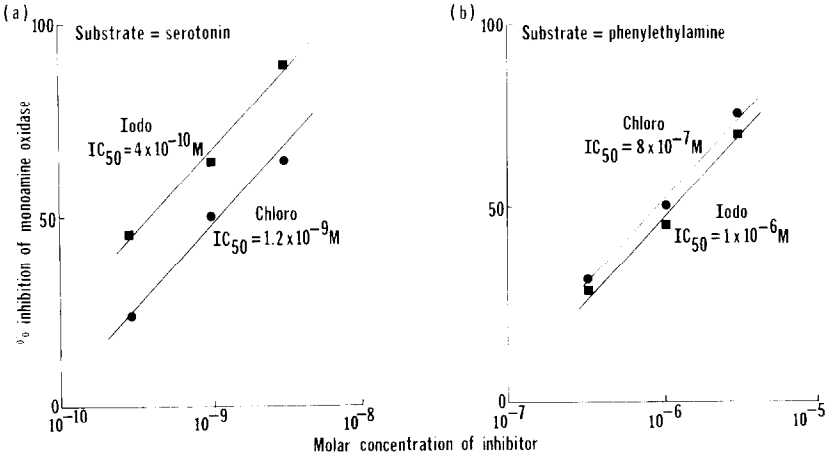

Fig. 2. Inhibition of (a) 100 μM [^{14}C]serotonin oxidation and (b) 12.5 μM [^{14}C]phenylethylamine oxidation by rat brain mitochondrial MAO. Squares represent LY121768, and circles represent LY51641. Inhibitors were preincubated with enzyme for 15 min prior to substrate addition. Each point is the average of two determinations at that inhibitor concentration.

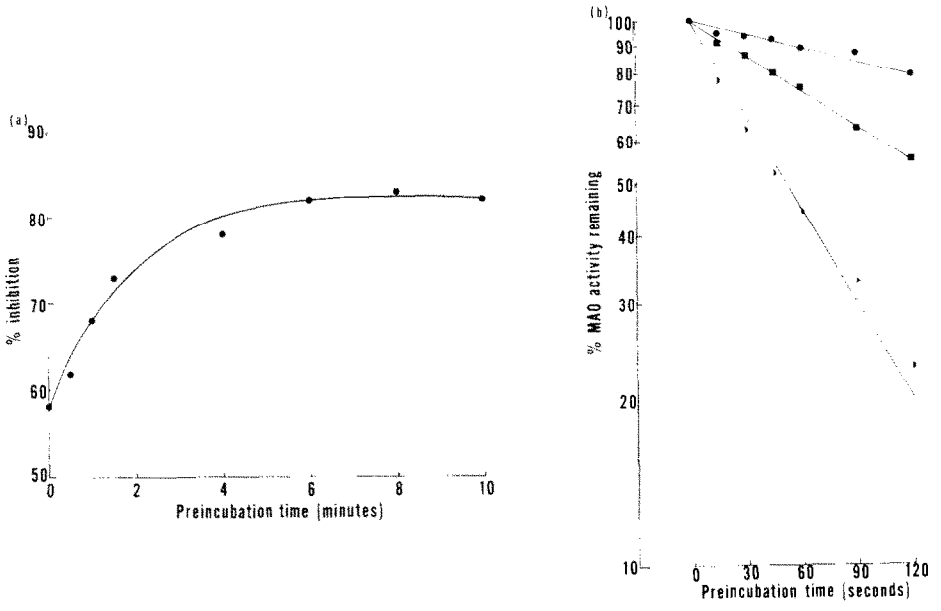

Fig. 3. Time-dependent inactivation of rat liver mitochondrial MAO by LY121768 with 100 μM [^{14}C]serotonin as substrate. (a) Plot of percent inhibition against time of preincubation of enzyme and inhibitor (10^{-9} M LY121768) prior to addition of substrate. (b) Plot of percent enzyme activity remaining (logarithmic scale) against time of preincubation of enzyme and inhibitor during the initial period of first-order reaction. The concentrations of LY121768 incubated with enzyme were 3×10^{-9} M (●), 1×10^{-8} M (■), and 3×10^{-8} M (◑). The enzyme–inhibitor solution was then diluted 15-fold in the assay incubation mixture.

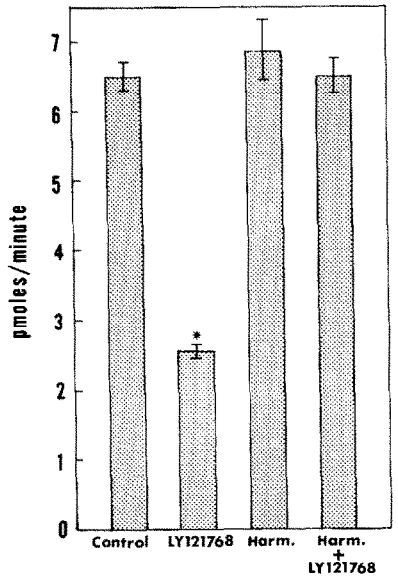

Fig. 4. Effect of the presence of harmaline on the inhibition of rat liver mitochondrial MAO by LY121768 after dialysis. Enzyme was incubated with 1×10^{-8} M LY121768 alone or in the presence of 1×10^{-7} M harmaline for 15 min and then dialyzed for 22 hr at 4° against 0.001 M sodium phosphate buffer, pH 7.4. During the first 6 hr of dialysis, harmaline (1×10^{-7} M) was present in the dialyzing buffer. MAO activity was assayed with 100 μM [^{14}C]serotonin as substrate. The asterisk (*) indicates a significant difference from control ($P < 0.05$).

tion dependent at 3×10^{-9}, 1×10^{-8}, and 3×10^{-8} M concentrations of LY121768.

When LY121768 (1×10^{-8} M) was incubated with MAO for 15 min at 37° prior to extensive dialysis in the cold, inhibition of type A MAO persisted after dialysis (Fig. 4). Harmaline, added at a concentration (10^{-7} M) that inhibits type A MAO by 80–90% without dialysis, produced no inhibition after dialysis. Not only was the inhibition by harmaline completely reversed by dialysis, but the addition of harmaline along with LY121768 completely prevented the irreversible inhibition by LY121768, indicating that enzyme activity was necessary for the time-dependent inactivation of MAO by LY121768.

In vivo *studies*. The activities of type A and type B MAO in rat brain, heart and liver were measured at times of 1–24 hr after the administration of LY121768 at a dose of 10 mg/kg i.p. to rats (Table 1). MAO activity in brain was inhibited more than 90% at times from 1 to 8 hr and showed little recovery at 24 hr. In contrast, type B MAO was not affected significantly by this dose of LY121768 at any of these times. In liver, the percent inhibition of type A MAO was only slightly less than in brain at early times, though somewhat more recovery of enzyme activity had occurred by 24 hr. No significant inhibition of type B MAO was found in liver. The inhibition of type A MAO in heart was similar to that in brain. In rat heart, phenylethylamine oxidation occurs primarily by type A MAO [10], and substantial inhibition of phenylethylamine oxidation, persisting still at 24 hr, was therefore observed in heart.

Table 1. Effect of LY121768 on MAO activity in rat tissues at early times

Hr after LY121768 (10 mg/kg, i.p.)	MAO activity (nmoles·g^{-1}·min^{-1}) Brain		Heart		Liver	
	Serotonin	Phenylethylamine	Serotonin	Phenylethylamine	Serotonin	Phenylethylamine
0	81 ± 1	33 ± 1	67 ± 1	9 ± 1	329 ± 8	270 ± 14
1	2 ± 0.3* (−97%)	32 ± 1	1 ± 0.2* (−98%)	4 ± 0.1* (−56%)	35 ± 3* (−89%)	244 ± 7
2	3 ± 0.4* (−96%)	33 ± 1	1 ± 0.2* (−98%)	5 ± 0.2* (−44%)	52 ± 7* (−84%)	259 ± 8
4	3 ± 0.4* (−96%)	35 ± 1	2 ± 0.4* (−97%)	4 ± 0.1* (−56%)	67 ± 3* (−80%)	235 ± 11
8	6 ± 0.5* (−93%)	33 ± 1	3 ± 0.4* (−96%)	5 ± 0.2* (−44%)	80 ± 5* (−76%)	264 ± 10
24	15 ± 0.5* (−81%)	34 ± 1	12 ± 2* (−82%)	5 ± 0.1* (−44%)	160 ± 7* (−51%)	266 ± 13

* Significant decrease from zero time ($P < 0.05$).

Figure 5 shows the dose-dependence of the inhibition of type A MAO by LY121768 in these three tissues. The calculated ED_{50} values were 0.4, 0.3 and 0.95 mg/kg for brain, heart and liver respectively.

Table 2 shows that harmaline was capable of antagonizing the inactivation of type A MAO *in vivo* as it had done *in vitro*. In the first experiment, the degree of antagonism by harmaline was shown to be dose dependent. The lowest dose of harmaline (0.1 mg/kg) had no significant effect on the percent inhibition by LY121768. The 1 and 10 mg/kg doses of harmaline significantly antagonized the inhibition by LY121768 in brain and in liver, and the degree of antagonism was greater at the higher dose. In heart, only the 10 mg/kg dose showed a significant effect. In the second experiment, a lower dose of LY121768 and a higher dose of harmaline were used, and in this experiment harmaline completely protected against the inhibition by LY121768 in all three tissues.

The effects of LY121768 at longer times are shown in Table 3. Significant inhibition of type A MAO in brain persisted still at 7 days after the single 10 mg/kg dose. No inhibition of type B MAO was seen at any time, consistent with the data in other experiments. Hypothalamic concentrations of dopamine, norepinephrine and epinephrine were increased significantly at all times after LY121768, the largest percentage changes occurring at the 1-day time when percent inhibition of type A MAO was highest. The concentrations of the two major metabolites of dopamine in rat brain, DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid), were decreased, the largest decreases occurring at day 1.

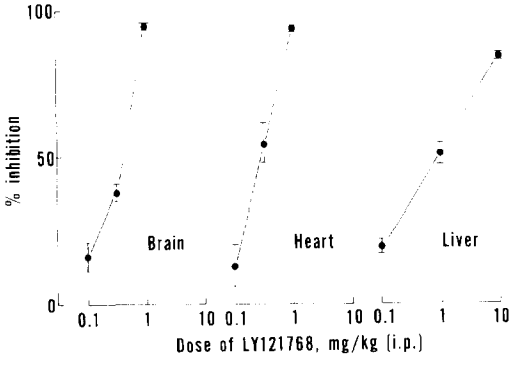

Fig. 5. Inhibition of type A MAO in rat tissues *in vivo* by LY121768. MAO activity was assayed in tissue homogenates with [^{14}C]serotonin as substrate 1 hr after the i.p. injection of LY121768 at the doses indicated.

DISCUSSION

The inhibition of MAO by *N*-cyclopropyl amines, like that by *N*-propargyl amines and hydrazines [11–13], is believed to occur through a "k_{cat}" mechanism, in which irreversible inhibition of the enzyme results from catalytic conversion of the inhibitor to a reactive intermediate species that reacts covalently with a functional group on the enzyme [14–17]. All of the studies described here are consistent with the expectation that LY121768 would be an irreversible inhibitor of MAO. The inability of dialysis to restore enzyme activity and the increase in percent inhibition with time of preincubation with the enzyme are characteristic of irreversible inhibitors. The long-lasting inhibition of type A MAO *in vivo* and the ability of harmaline to prevent that effect suggest that LY121768 irreversibly inactivated type A MAO *in vivo* as well as *in vitro*.

The fact that harmaline prevented the inactivation of type A MAO by LY121768 both *in vitro* and *in vivo* indicates that the inactivation of the enzyme was dependent upon enzyme catalysis. Presumably harmaline prevented type A MAO from acting on LY121768 to form an intermediate product that was reactive toward the enzyme. The ability of harmaline to antagonize the inactivation of type A MAO *in vivo* has long been known [18, 19] and has been used previously to alter the selectivity of MAO inhibitors [20], since harmaline is very weak as an inhibitor of type B MAO *in vitro* and has little or no effect on type B MAO *in vivo*. Pargyline, for example, has slight selectivity in inhibiting type B MAO normally but, when given in combination with harmaline, produces a highly selective inactivation of type B

Table 2. Dose-dependent prevention by harmaline of the inactivation of type A MAO *in vivo* by LY121768*

Treatment group	MAO activity with [^{14}C]serotonin as substrate (nmoles·g^{-1}·min^{-1}) Brain	Heart	Liver
Experiment 1			
Control	101 ± 1	86 ± 4	334 ± 12
LY121768 (3 mg/kg)	38 ± 3†	29 ± 5†	225 ± 7†
LY121768 + harmaline (0.1)	31 ± 3†	25 ± 4†	233 ± 7†
LY121768 + harmaline (1)	61 ± 5†‡	33 ± 8†	289 ± 6†‡
LY121768 + harmaline (10)	87 ± 2†‡	76 ± 6‡	303 ± 3†‡
Experiment 2			
Control	87 ± 2	79 ± 5	300 ± 11
LY121768 (1 mg/kg)	28 ± 1†	30 ± 3†	241 ± 1†
LY121768 + harmaline (20)	83 ± 2‡	81 ± 6‡	312 ± 12‡

* Rats were killed 24 hr after the i.p. injection of LY121768 alone or with harmaline (at the mg/kg doses indicated parenthetically).
† Significant difference from control ($P < 0.05$).
‡ Significant difference from group with LY121768 alone ($P < 0.05$).

MAO because its inactivation of type A MAO is prevented [20, 21]. Harmaline in a dose-dependent manner antagonized the inactivation of type A MAO by LY121768, and with the proper ratio of doses of harmaline and LY121768 the inactivation was prevented completely (Table 1).

Not only is LY121768 more selective than LY51641 *in vitro*, but the same difference is seen *in vivo*, since LY51641 has been found to produce some inhibition of type B MAO when doses adequate to inhibit type A MAO completely are used [4, 22]. The current data show that LY121768 can be given at doses that produce more than 90% inhibition of type A MAO in brain without detectable inhibition of type B MAO. As with LY51641 [22], the inhibition of type A MAO by LY121768 was somewhat greater in brain than in liver.

The elevation of hypothalamic concentrations of dopamine, norepinephrine and epinephrine and the lowering of dopamine metabolites by LY121768 further add to the already compelling evidence that these catecholamines are oxidized in rat brain almost exclusively by type A MAO (see [23] for references).

The unsubstituted *N*-cyclopropyl-phenoxyethylamine, lacking a chloro or iodo substituent in the *ortho* position of the phenyl ring, is less potent and less selective as an inhibitor of type A MAO than is either LY51641 or LY121768 [24]. The iodo substituent not only confers selectivity for type A MAO but also represents a site for potential introduction of a radionuclide into a molecule expected to attach irreversibly to type A MAO. There is no reason to expect that such attachment would occur to any other macromolecule, since catalytic activation of the molecule by MAO appears to be an essential step. This suggests that LY121768 could be a useful tool for irreversibly labeling type A MAO with high specificity both *in vitro* and *in vivo*.

The are two possible problems to be considered in relation to the use of LY121768 as a label for type A MAO. One concerns the stability of the adduct that is formed with the enzyme. Silverman and Hoffman [15, 16] have shown that the adducts formed by *N*-cyclopropyl-*N*-arylalkylamines are not as stable as those formed by propargyl amines or by hydrazines with MAO. The adducts dissociate *in vitro* upon dialysis at pH 9 or upon addition of a substrate like benzylamine. Thus, there is the possibility that

Table 3. Duration of the effects of LY121768 on MAO activity, catecholamine concentrations, and dopamine metabolites in rat brain*

Days after LY121768 injection	MAO activity (nmoles/g/min) Serotonin	Phenylethylamine	Catecholamine (nmoles/g) Dopamine	Norepinephrine	Epinephrine	Dopamine metabolites (nmoles/g) DOPAC	HVA
0	88 ± 1	31 ± 0.5	1,019 ± 94	7,379 ± 94	126 ± 9	151 ± 6	94 ± 4
1	19 ± 1 (−78%)	31 ± 0.4	1,476 ± 53 (+45%)	11,408 ± 385 (+55%)	387 ± 14 (+206%)	83 ± 4 (−45%)	58 ± 3 (−40%)
3	43 ± 2 (−52%)	31 ± 0.3	1,378 ± 42 (+35%)	10,285 ± 349 (+39%)	397 ± 32 (+214%)	109 ± 4 (−28%)	78 ± 3 (−19%)
5	39 ± 4 (−56%)	30 ± 1	1,200 ± 32 (+18%)	9,522 ± 308 (+29%)	325 ± 20 (+157%)	114 ± 6 (−25%)	81 ± 7
7	58 ± 2 (−34%)	33 ± 2	1,218 ± 62 (+20%)	9,094 ± 358 (+23%)	282 ± 19 (+123%)	120 ± 5 (−20%)	77 ± 4 (−20%)

* LY121768 was injected i.p. at 10 mg/kg. Catecholamines were measured in hypothalamus, dopamine metabolites in cerebral hemispheres, and MAO activity in the remaining brain tissue. Parenthetic numbers show percent changes for all groups that differed significantly ($P < 0.05$) from control.

the label on type A MAO formed by LY121768 would not be stable to some conditions of proteolysis, for example, and this would affect the usefulness of the compound as a means of introducing a label for subsequent identification of a peptide fragment in *in vitro* studies. If this were a problem, it apparently could be solved by adding a methyl group to the cyclopropyl moiety, since compounds of this type form very stable addition products with MAO [25]. There should be no problem *in vivo*, since the fact that type A MAO activity was inhibited for at least 7 days following a single dose of LY121768 is evidence for the stability of the adduct. So even if these molecules do form complexes that are labile to *in vitro* manipulation, they apparently are stable *in vivo*.

A second possible problem is that the molecule with the radioisotope in the position proposed might not label the enzyme at all. Singer [14] postulated two possible structures for the adduct formed between tranylcypromine and MAO, one involving a thioaminoketal structure and the other involving a thiohemiketal structure. In the latter case, the nitrogen has been lost while the cyclopropyl moiety remains attached to the enzyme. With LY121768, the proposed iodine label is on a group attached to the nitrogen, so if the nitrogen were lost the radioactive label would also be lost despite persistence of MAO inhibition. However, Silverman and Hoffman [16] have shown that a radiocarbon label on the phenyl moiety of *N*-cyclopropyl-benzylamine does remain attached to MAO, so this is evidence that, with *N*-cyclopropyl-*N*-arylalkylamines, the nitrogen does remain coupled to the site of attachment to the enzyme, although the thiohemiketal structure considered by Singer might occur with the primary amine, tranylcypromine.

Inhibitors in radioactive form have been used previously to label MAO. Tritiated harmaline has been evaluated as a radioligand for reversible labeling of type A MAO [26, 27]. Tritiated pargyline has been used to label MAO irreversibly in experiments aimed at isolating labeled peptide fragments after proteolysis of the enzyme [28, 29] and for quantitation of the number of MAO molecules [30]. Pargyline is not highly selective as an MAO inhibitor. The use of radioactive LY121768 for labeling type A MAO selectively could have application in studies of the above type. After administration of radiocarbon-labeled pargyline to rats, the recovery of MAO activity in liver (due to synthesis of new enzyme) was shown to parallel the disappearance of radioactivity during the next 11 days [31]. LY121768 in radioactive form should be useful in studies of this sort to measure the turnover of type A MAO specifically. This turnover may vary with tissue and species [32] and has been studied in relatively few cases.

Numerous isotopes of iodine are available, and these differ markedly in the nature of radiation emitted and in half-life. Radioiodine-containing labels have been useful in autoradiography, scintigraphic imaging, and single photon emission-computed tomography [33–36]. The possibility of using appropriately labeled LY121768 for location and quantitation of type A MAO, for monitoring the duration of

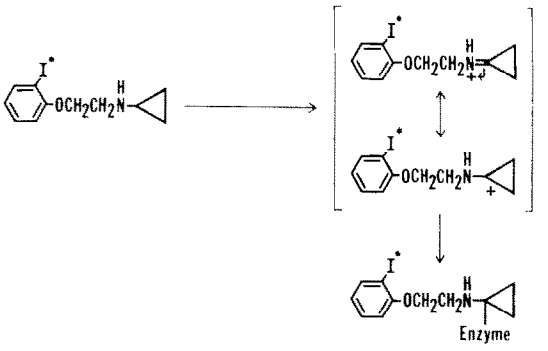

Fig. 6. Postulated mechanism by which LY121768 containing a radioisotope of iodine (*) could be used to label type A MAO irreversibly (based on Refs. 16 and 17). LY121768 is acted upon by type A MAO, oxidizing the cyclopropyl carbon attached to the nitrogen. The highly reactive cyclopropanone imine is formed, which reacts with a nucleophilic (possibly sulfhydryl-containing) group at or near the active site of the enzyme. Paech *et al.* [17] have presented evidence that suicide inhibition of MAO by cyclopropylamines involves an amino acid component of the enzyme rather than the flavin.

enzyme inhibition, and for determining the rate of turnover of the enzyme, all by noninvasive techniques appropriate for use in large animals including humans, can be considered. We have not synthesized radioactive LY121768 but would expect it to label type A MAO according to the mechanism supported by current evidence by which *N*-cyclopropyl arylalkylamines are thought to react with the enzyme (see Fig. 6). Harmaline prevention of labeling would be a means of verifying the site of labeling by LY121768 as type A MAO both *in vitro* and *in vivo*.

REFERENCES

1. N. H. Neff and H-Y. T. Yang, *Life Sci.* **14**, 2061 (1974).
2. C. J. Fowler, B. A. Callingham, T. J. Mantle and K. F. Tipton, *Biochem. Pharmac.* **27**, 97 (1978).
3. R. W. Fuller, *7th Int. Congr. Biochem.* (Abstr.), p. 999. Science Council of Japan, Ueno Park, Tokyo (1967).
4. R. W. Fuller and S. K. Hemrick, *Proc. Soc. exp. Biol. Med.* **158**, 323 (1978).
5. R. W. Fuller, I. H. Slater and J. Mills, in *Monoamine Oxidase: Structure, Function, and Altered Functions* (Eds. T. P. Singer, R. W. Von Korff and D. L. Murphy), p. 317. Academic Press, New York (1979).
6. R. J. Wurtman and J. Axelrod, *Biochem. Pharmac.* **12**, 1439 (1963).
7. R. W. Fuller, B. J. Warren and B. B. Molloy, *Biochem. Pharmac.* **19**, 2934 (1970).
8. R. W. Fuller and K. W. Perry, *Biochem. Pharmac.* **26**, 2087 (1977).
9. K. W. Perry and R. W. Fuller, *Soc. Neurosci. Abstr.* **5**, 348 (1979).
10. G. A. Lyles and B. A. Callingham, *J. Pharm. Pharmac.* **27**, 682 (1975).
11. R. R. Rando, *Science* **185**, 320 (1974).
12. W. C. Kenney, J. Nagy, J. I. Salach and T. P. Singer, in *Monoamine Oxidase: Structure, Function, and Altered Functions* (Eds. T. P. Singer, R. W. Von Korff and D. L. Murphy), p. 25. Academic Press, New York (1979).
13. C. J. Fowler, L. Oreland and B. A. Callingham, *J. Pharm. Pharmac.* **33**, 341 (1981).

14. T. P. Singer, in *Monoamine Oxidase: Structure, Function, and Altered Functions* (Eds. T. P. Singer, R. W. Von Korff and D. L. Murphy), p. 7. Academic Press, New York (1979).
15. R. B. Silverman and S. J. Hoffman, in *Monoamine Oxidase: Structure, Function, and Altered Functions* (Eds. T. P. Singer, R. W. Von Korff and D. L. Murphy), p. 71. Academic Press, New York (1979).
16. R. B. Silverman and S. J. Hoffman, *J. Am. chem. Soc.* **102**, 884 (1980).
17. C. Paech, J. I. Salach and T. P. Singer, *J. biol. Chem.* **255**, 2700 (1980).
18. A. Pletscher and H. Besendorf, *Experientia* **15**, 25 (1959).
19. A. Horita and W. R. McGrath, *Biochem. Pharmac.* **3**, 206 (1960).
20. R. W. Fuller and S. K. Hemrick, *Life Sci.* **22**, 1083 (1978).
21. R. W. Fuller, S. K. Hemrick-Luecke and K. W. Perry, *Biochem. Pharmac.* **30**, 1295 (1981).
22. R. W. Fuller, S. K. Hemrick and J. Mills, *Biochem. Pharmac.* **27**, 2255 (1978).
23. R. W. Fuller and S. K. Hemrick-Luecke, *Res. Commun. Chem. Path. Pharmac.* **32**, 207 (1981).
24. D. L. Murphy, C. H. Donnelly, E. Richelson and R. W. Fuller, *Biochem. Pharmac.* **27**, 1767 (1978).
25. R. B. Silverman and S. J. Hoffman, *Biochem. biophys. Res. Commun.* **101**, 1396 (1981).
26. D. L. Nelson, A. Herbet, Y. Petillot, L. Pichat, J. Glowinski and M. Hamon, *J. Neurochem.* **32**, 1817 (1979).
27. D. L. Nelson, A. Herbet, J. Glowinski and M. Hamon, *J. Neurochem.* **32**, 1829 (1979).
28. R. M. Cawthon, J. E. Pintar, F. P. Haseltine and X. O. Breakefield, *J. Neurochem.* **37**, 363 (1981).
29. P. H. Yu, *Can. J. Biochem.* **59**, 30 (1981).
30. D. Parkinson and B. A. Callingham, *J. Pharm. Pharmac.* **32**, 49 (1980).
31. V. G. Erwin and R. A. Deitrich, *Molec. Pharmac.* **7**, 219 (1971).
32. L. Della Corte and K. F. Tipton, *Biochem. Pharmac.* **29**, 891 (1980).
33. W. B. Myers, in *Radioactive Pharmaceuticals* (Eds. G. A. Andrews, R. M. Kniseley and H. N. Wagner, Jr.), p. 217. U.S. Atomic Energy Commission, Washington, DC (1966).
34. H. S. Winchell, R. M. Baldwin and T. H. Lin, *J. nucl. Med.* **21**, 940 (1980).
35. H. S. Winchell, W. D. Horst, L. Braun, W. H. Oldendorf, R. Hattner and H. Parker, *J. nucl. Med.* **21**, 947 (1980).
36. T. C. Hill, B. L. Holman, R. Lovett, D. H. O'Leary, D. Front, P. Magistretti, R. E. Zimmerman, S. Moore, M. E. Clouse, J. L. Wu, T. H. Lin and R. M. Baldwin, *J. nucl. Med.* **23**, 191 (1982).