*Biochemical Pharmacology*, Vol. 35, No. 8, pp. 1381–1387, 1986.
Printed in Great Britain.

0006-2952/86 $3.00 + 0.00


# INHIBITION OF MONOAMINE OXIDASE IN MONOAMINERGIC NEURONES IN THE RAT BRAIN BY IRREVERSIBLE INHIBITORS

INGRID FAGERVALL and SVANTE B. ROSS*
Research Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden

(*Received* 3 *June* 1985; *accepted* 5 *November* 1985)

**Abstract**—The irreversible inhibition of monoamine oxidase (MAO) inside and outside monoaminergic neurones in the rat brain by the suicide inhibitors clorgyline, selegiline (*l*-deprenyl), pheniprazine, phenelzine, iproniazid, pargyline and the *d*- and *l*-enantiomers of tranylcypromine was determined. This was achieved by incubating crude synaptosomal preparations of hypothalamus and striatum from rats treated with the inhibitors 24 hr earlier, with low concentrations of [$^{14}$C]serotonin (0.1 $\mu$M), [$^{14}$C]-noradrenaline (0.25 $\mu$M) and [$^{14}$C]dopamine (0.25 $\mu$M) in the absence and presence of selective uptake inhibitors (citalopram, maprotiline and amfonelic acid, respectively). It was found that all inhibitors inhibited the deamination of serotonin and noradrenaline outside the amine neurons at slightly lower doses than that within these neurones. This could at least in part be due to protection of MAO by the endogenous amines in these neurones. The deamination of dopamine was rather more strongly inhibited inside the neutrons than outside, particularly at higher doses. There was no indication that tranylcypromine or phenelzine was accumulated in the neurones by the membranous amine uptake mechanisms. The rate of the recovery of the deaminating activities inside and outside the serotonergic and noradrenergic neurones in hypothalamus after phenelzine and clorgyline inhibition was the same (50% recovery after 12–15 days), which indicates similar rate of synthesis of MAO in different cell types.

Although the enzyme monoamine oxidase (MAO) (EC 1.4.3.4) occurs in all mitochondria-containing cells, MAO localized in the monoamine neurones has attracted particular attention, since it takes part in the regulation of the monoamine levels and thereby the neurotransmission in the monoamine systems. The antidepressant action of MAO inhibitors has been explained as the result of an increased release of the transmitter amines or, as a consequence of this increase, down-regulation of postsynaptic receptor responses (for review see [1]). Since the monoaminergic neurones constitute a very small part of all neurones and cells in the brain it has been impossible to measure the MAO activity in these neurones separate from that in other cells. Thus, chemical or electrolytic destruction of dopaminergic neurones did not change the MAO activity in striatal preparation when measured with conventional methods, although the tyrosine hydroxylase activity, a marker for dopamine nerve terminals in this region, was almost abolished [2]. However, when the deaminating activity is measured in a preparation with intact synaptosomes, and with a low concentration of dopamine as substrate, the decrease in MAO activity due to the destruction of dopaminergic nerve terminals can be demonstrated [3].

The development of selective inhibitors of the monoamine re-uptake mechanisms has made it possible to measure the deaminating activity in synaptosomes of the various monoaminergic systems separately from each other and from synaptosomes of other origin [4–6]. This technique utilizes low concentration of the [$^{14}$C]labelled monoamine which is accumulated in the synaptosomes by the specific active uptake mechanism. The difference between the deaminating activity in the absence and presence of a selective uptake inhibitor is a measure of the deamination of the amine within the specific aminergic synaptosomes. In the present study we have examined the irreversible inhibitory actions on MAO inside and outside neurones in the rat brain *in vivo* by the acetylenic MAO inhibitors clorgyline, which inhibits selectively the A-form of MAO [7], selegiline (*l*-deprenyl) which is a selective MAO-B inhibitor [8] and pargyline which has some preference on the B-form [9], the hydrazine derivatives pheniprazine, phenelzine and iproniazid, which are nonselective inhibitors and the *l*- and *d*-enantiomers of the cyclopropyl derivative tranylcypromine, a nonselective inhibitor.

We have also examined the rate of resynthesis of MAO inside and outside serotonergic and noradrenergic nerve terminals in the rat hypothalamus after irreversible inhibition by phenelzine and clorgyline.

## MATERIALS AND METHODS

*Materials.* Dopamine [7-$^{14}$C]hydrochloride (57 mCi/mmole), l-noradrenaline [8-$^{14}$C]hydrogen tartrate (57 mCi/mmole) and 5-hydroxytryptamine [side chain-2-$^{14}$C]creatinine sulphate (61 mCi/mmole) were purchased from Amersham International plc, U.K. Clorgyline hydrochloride was synthesized by L. Florvall, Astra Läkemedel AB. Selegiline (*l*-deprenyl) hydrochloride was kindly donated by Professor J. Knoll, Semmelweis University, Budapest, Hungary, the *d*- and *l*-enantiomers of tran-

* To whom all correspondence should be addressed.

ylcypromine by Dr C. Kaiser, Smith, Kline & French Laboratories, Philadelphia, U.S.A., and pheniprazine hydrochloride by Dr K. Wetterlind, AB Draco, Lund, Sweden. Pargyline hydrochloride was bought from Saber Laboratories, U.S.A. and phenelzine hydrochloride from Sigma Chemical Company, St Louis, U.S.A. Amfonelic acid was bought from Research Biochemical Incorporated, Wayland, Mass., U.S.A. Citalopram hydrobromide and maprotiline hydrochloride were gifts from Lundbeck and Co A/S Copenhagen, Denmark and Ciba Geigy AG, Basel, Switzerland, respectively.

Male Sprague–Dawley rats weighing 160–200 g were used. They were housed in groups of four and were freely supplied with food and water. The injections were performed subcutaneously with solutions of the compounds in 0.9% NaCl in a volume of 1 ml/kg body weight. The animals were killed by decapitation 24 hr after the injection.

*Tissue preparation.* Hypothalamus or striatum from each rat was rapidly dissected out, weighed and homogenized in an all-glass homogenizer with 20 vol. of ice-chilled 0.25 M sucrose. The homogenates were centrifuged at 800 *g* for 10 min and the synaptosome-rich supernatants were used in the assay.

*Monoamine oxidase activity.* The monoamine oxidase activity inside and outside the aminergic synaptosomes was determined as described previously [5] but with some modifications. In the serotonin experiments 50 μl of the synaptosomal preparation from hypothalamus corresponding to 2.5 mg wet wt tissue was added to a glass-stoppered centrifuge tube containing 925 μl of Krebs–Henseleit's buffer, pH 7.4, equilibrated with 93.5% $O_2$ and 6.5% $CO_2$ and containing 5.4 mM glucose, 1.1 mM ascorbic acid, 0.13 mM EDTA $Na_2$, 1 μM maprotiline and 0.3 μM amfonelic acid. Each preparation was examined in duplicate without citalopram and in duplicate with 0.12 μM citalopram. After 10 min incubation in a water bath at 37° 25 μl of [$^{14}$C]serotonin (0.1 μM final concentration) was added and the incubation was continued for 10 min. The reaction was stopped by addition of 1 ml of 1 M HCl. The [$^{14}$C]5-hydroxyindoleacetic acid (5-HIAA) formed was extracted into 6 ml of ethyl acetate by vigorous shaking for 2 × 1 min in a multi-tube vortexer (model 2601, Scientific Manufacturing Industries, Emeryville, CA). After centrifugation 4 ml of the organic layer was taken into 10 ml Econofluor (NEN) and 1 ml ethanol and the radio-activity was measured in a Packard Tri Carb scintillation counter. The rate of the deamination is expressed as nmole [$^{14}$C]5-HIAA formed per g wet wt tissue per 10 min incubation.

In the noradrenaline experiments 200 μl of the hypothalamic synaptosomal preparation was used. The incubation medium (1.0 ml final volume) contained 0.25 μM [$^{14}$C]noradrenaline and 0.12 μM citalopram in order to hinder uptake of noradrenaline into serotonergic synaptosomes (amfonelic acid is not possible to use, since it also inhibits the uptake of noradrenaline [5]). Each synaptosomal preparation was assayed in the absence and presence of 3 μM maprotiline, a selective noradrenaline uptake inhibitor. The incubation and extraction were performed as described for the serotonin experiments. The extraction recovery of the product formed ([$^{14}$C]-DOPEG) was 33% ± 0.8 (S.D.) [5]. More than 80% of the radioactivity formed was [$^{14}$C]DOPEG, as shown from the partition between ethyl acetate and water at pH 8.6, and chromatography on alumina.

In the dopamine experiments the incubation medium contained 50 μl of the striatal preparation, 0.25 μM [$^{14}$C]DA, 0.12 μM citalopram and 3 μM maprotiline. The assay was performed in duplicate in the absence and presence of 0.3 μM amfonelic acid. The incubation and extraction procedures were the same as for the serotonin experiments. Under the conditions used the deamination was linear for at least 10 min for all three substrates.

The deamination of $^{14}$C-amine in the presence of the selective uptake inhibitor was assumed to be occurring outside aminergic synaptosomes. The difference between the activities obtained in the absence and presence of the uptake inhibitor was regarded to be that occurring within the aminergic synaptosomes. The uptake inhibitors had no MAO inhibitory effect at the concentrations used. The $K_i$ values for the inhibition of the amine uptake by the compounds used are given in Table 1.

Table 1. Inhibitor constants ($K_i$) for the uptake inhibitors used*

| | $K_i$ (μM) | | |
|---|---|---|---|
| | 5-HT | NA | DA |
| Citalopram | 0.004 | 5.0 | >10 |
| Maprotiline | 17 | 0.03 | >10 |
| Amfonelic acid | 3.5 | 0.04 | 0.03 |

* The constants were estimated from $IC_{50}$ values at 0.05 μM of the labelled amines and the apparent $K_m$ values 0.05, 0.1 and 0.1 μM for respective 5-HT, NA and DA according to the formula for competitive inhibition:

$$K_i = \frac{IC_{50}}{1 + \frac{[S]}{K_m}}$$

## RESULTS

### *Dose–response courses for irreversible MAO inhibitors*

The irreversible inhibition of MAO in the rat brain was determined 24 hr after the subcutaneous injection of the compounds.

*Clorgyline.* At low doses clorgyline produced significantly less inhibition of MAO within serotonergic and noradrenergic nerve terminals in the hypothalamus than outside these neurones (Fig. 1A). This difference between the inhibition outside and inside the aminergic nerve terminals was not so apparent in the striatum. At high doses the inhibition within dopamine and noradrenaline terminals exceeded that outside these terminals. The inhibition courses outside the terminals appear to be biphasic for all three substrates with the second phase appearing above 80% inhibition. However, the main part of the inhibition for all three substrates occurred at MAO-A inhibitory doses of clorgyline with $ED_{50}$ values between 0.1 and 0.2 mg/kg s.c.

*Selegiline.* The selective MAO-B inhibitor sele-

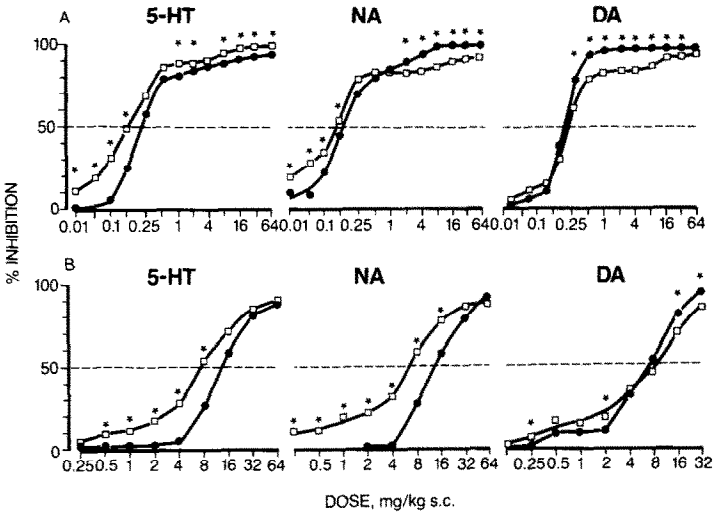


Fig. 1. Dose–response curves for the inhibition by clorgyline (A) and selegiline (B) of the deamination of serotonin (5-HT) and noradrenaline (NA) by hypothalamic preparations and dopamine (DA) by striatal preparations. The compounds were injected 24 hr before the sacrifice of the rats. Each dose was given to four rats. Deamination of the substrates inside (●) and outside (○) the aminergic neurones was determined as described in Materials and Methods. The asterisks denote significant difference between neuronal and extraneuronal inhibition ($P < 0.05$, Mann–Whitney $U$-test).

giline inhibited the main part of the deamination of all three substrates at high, MAO-A inhibitory doses ($ED_{50}$ around 10 mg/kg s.c.) (Fig. 1B). The inhibition was significantly higher outside than inside the noradrenergic and serotonergic nerve terminals in the hypothalamus. The inhibition outside and inside dopaminergic nerve terminals in the striatum did not show this difference, although there was a tendency for slightly higher inhibition outside the nerve terminals at low doses and vice versa at higher doses of selegiline. A small part of the inhibition (10–20%) outside the aminergic neurones occurred at doses lower than 1 mg/kg which is in the dose–response range for the inhibition of MAO-B. At these low doses a small fraction (~10%) of MAO within the dopamine nerve terminals was inhibited whereas no low-dose inhibition within serotonergic and noradrenergic terminals was observed.

*Iproniazid, pargyline, phenelzine and phenipra-zine.* These non-selective MAO-inhibitors were, in the lower dose ranges, slightly more potent in inhibiting MAO outside the serotonergic and noradrenergic nerve terminals in the hypothalamus than inside these terminals (Figs 2 and 3). The opposite relationship was observed for the inhibition of the deamination of dopamine in striatum. The possibility that the preference for dopaminergic MAO was due to accumulation of the compounds by the dopamine uptake mechanism was examined for phenelzine. The dopamine uptake inhibitor amfonelic acid [10] was injected at the dose of 2 mg/kg s.c. 15 min prior to phenelzine. This pretreatment of the animals did not change the irreversible inhibitory effect of phenelzine (data not shown).

*Enantiomers of tranylcypromine*

The *d*-enantiomer of tranylcypromine was 4–8 times more potent than the *l*-form in inhibiting MAO in the rat brain (Fig. 4) which is in accordance with previous findings [8]. The inhibition outside the serotonergic and noradrenergic nerve terminals was slightly higher than that inside these terminals. Both enantiomers were about twice as potent in inhibiting MAO inside the dopaminergic nerve terminals than outside these terminals.

The possibility that tranylcypromine is accumulated into the dopaminergic nerve terminals via the dopamine pump, thereby causing higher MAO inhi-

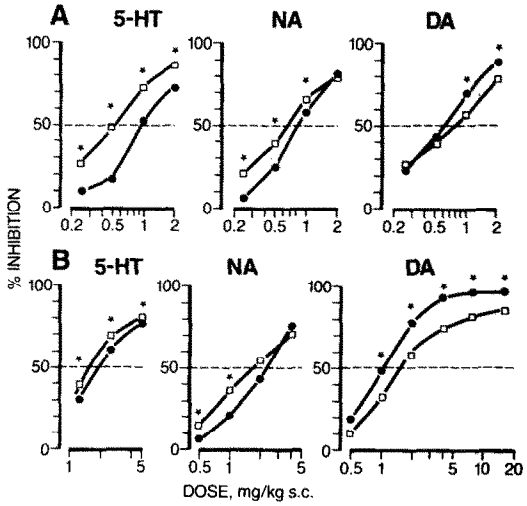


Fig. 2. Dose–response curves for the inhibition by phenipraZine (A) and phenelzine (B) of the deamination of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in synaptosomal preparations of rat hypothalamus and striatum inside (●) and outside (□) the aminergic neurones as described in the legend of Fig. 1 and in Materials and Methods.

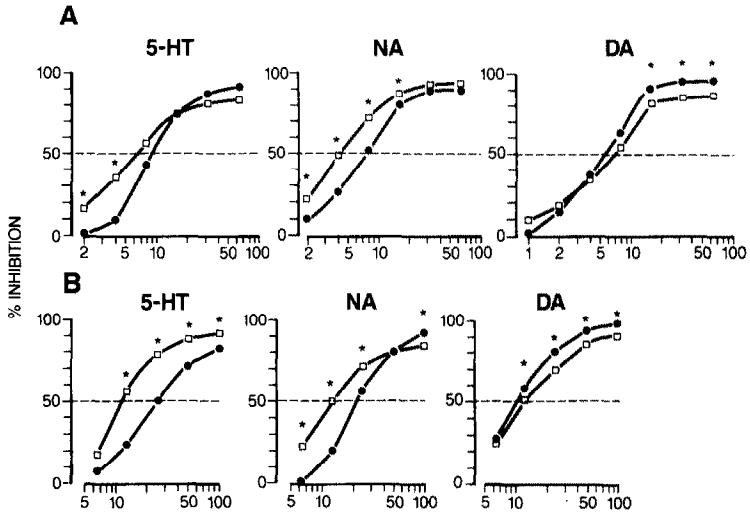


Fig. 3. Dose–response curves for the inhibition by pargyline (A) and iproniazid (B) of the deamination of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in synaptosomal preparations of rat hypothalamus and striatum inside (●) and outside (□) the aminergic neurones as described in the legend of Fig. 1 and in Materials and Methods.

bition inside than outside these terminals, was examined experimentally. The dopamine uptake inhibitor amfonelic acid, 2 mg/kg s.c., was injected 15 min before tranylcypromine and the monoamine deaminating activity was determined 24 hr later. The pretreatment did not change the MAO inhibition by the enantiomers within the dopaminergic terminals (data not shown). A similar experiment was performed with regard to MAO inhibition within serotonergic nerve terminals in the hypothalamus. In this case norzimeldine (20 mg/kg i.p.), a selective inhibitor of the neuronal serotonin uptake, was injected 15 min before tranylcypromine and MAO activity was assayed 24 hr later. The deaminating activities decreased similarly in the norzimeldine-treated and the control animals by tranylcypromine (data not shown).

*Effect of reserpine on the irreversible inhibition of MAO in the hypothalamus*

The difference between MAO inhibition inside and outside serotonergic and noradrenergic nerve terminals in the hypothalamus observed at low doses of the inhibitors may be due to a protective effect on MAO of the amines in these terminals against the irreversibly acting inhibitors. In order to examine this possibility the amines in the hypothalamus were depleted by a subcutaneous injection of reserpine,

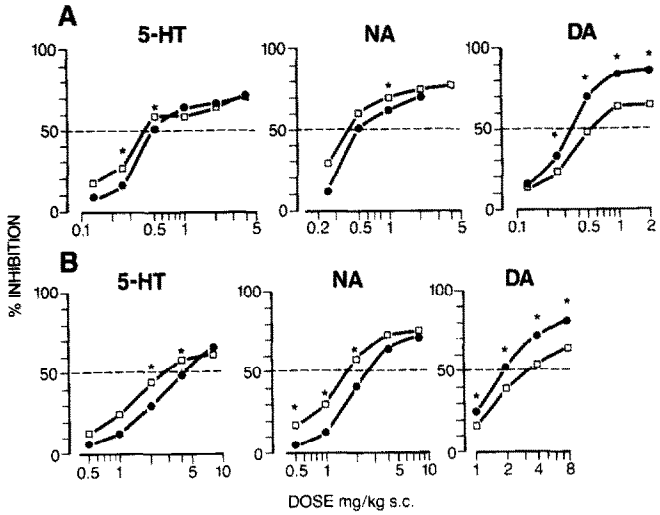


Fig. 4. Dose–response curves for the inhibition by *d*-tranylcypromine (A) and *l*-tranylcypromine (B) of the deamination of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in synaptosomal preparations of rat hypothalamus and striatum inside (●) and outside (□) the aminergic neurones as described in the legend of Fig. 1 and in Materials and Methods.

Table 2. Effect of reserpine pretreatment on the neuronal (N) and extraneuronal (EN) MAO inhibition*

| Compound | Dose (mg/kg s.c.) | % Inhibition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5-HT | | | | NA | | | |
| | | Saline | | Reserpine | | Saline | | Reserpine | |
| | | N | EN | N | EN | N | EN | N | EN |
| Clorgyline | 0.05 | 15 ± 2 | 37† ± 2 | 24 ± 1 | 41† ± 4 | 13 ± 6 | 39† ± 2 | 33 ± 1 | 37 ± 6 |
| Selegiline | 4 | 24 ± 5 | 59† ± 2 | 32 ± 3 | 57† ± 2 | 25 ± 2 | 59† ± 1 | 48 ± 1 | 65† ± 1 |
| Iproniazid | 12.5 | 49 ± 3 | 72† ± 1 | 25 ± 2 | 55† ± 5 | 45 ± 5 | 71† ± 2 | 36 ± 3 | 61† ± 6 |
| Pheniprazine | 0.5 | 7 ± 1 | 41† ± 3 | 12 ± 5 | 38† ± 2 | 7 ± 2 | 39† ± 4 | 33 ± 3 | 40 ± 3 |
| Control values (nmole/g/10 min) | | 2.89 ± 0.20 | 3.01 ± 0.05 | 4.56 ± 0.13 | 2.46 ± 0.09 | 1.33 ± 0.05 | 1.23 ± 0.02 | 2.65 ± 0.12 | 1.22 ± 0.04 |

* Reserpine, 5 mg/kg s.c., was given 18 hr before the MAO inhibitors and the rats were killed 24 hr after the latter injections. The amine deaminating activities of synaptosomal preparation of hypothalamus were determined as described in Materials and Methods. Each value is the mean ± S.E.M. from four rats.

† Significant difference EN vs N ($P < 0.05$, Mann–Whitney $U$-test).

5 mg/kg, 18 hr before the injection of the MAO inhibitors. Table 2 shows that the difference between the MAO inhibition outside and inside the serotonergic terminals also persisted after reserpine administration. However, for two of the inhibitors, clorgyline and pheniprazine, the difference between the degree of inhibition outside and inside the noradrenergic neurones disappeared after reserpine treatment. This change was due to an increased inhibition within the noradrenergic neurones whereas the inhibition outside these neurones was unchanged. Table 2 also shows that the rate of deamination of serotonin and noradrenaline was higher within the synaptosomes from the reserpine-pretreated control animals than within those from the non-pretreated animals, obviously due to the inhibition of the vesicular uptake of the amines within the synaptosomes.

*Time course of MAO inhibition by phenelzine and clorgyline*

The recovery of the deaminating activity after an irreversible MAO inhibitor is the result of the resynthesis of the enzyme. The half-life of MAO can be estimated from the time course of the disappearance of the inhibition [11, 12]. It was of interest to examine if there is any difference in the half-life of MAO in the specific aminergic neurones compared to that in other cells. Rats were therefore treated subcutaneously with phenelzine (4 mg/kg) or clorgyline (0.5 mg/kg) and the deaminating activities of crude synaptosomal preparations of hypothalamus were compared with that from saline-treated rats at various times after the administration. As shown in Fig. 5, there was no apparent difference in the disappearance of the MAO inhibition inside or outside serotonergic and noradrenergic nerve terminals in the hypothalamus. The half-life of MAO estimated from the time courses was 12–15 days. However, the recovery of the enzyme activity did not appear to follow first-order kinetics as expected, since the rate of recovery tended to decrease with time.

## DISCUSSION

The present study was undertaken in order to examine the effect of irreversibly acting MAO inhibitors on MAO within monoamine neurones in the rat brain. In order to avoid the reversible effect of the drugs the assay was made 24 hr after their administration. The MAO inhibition within the aminergic neurones was measured as the difference between the deamination of the amine by a synaptosomal preparation in the absence and presence of selective uptake inhibitors. At the low concentrations the [$^{14}$C]labelled amines employed about 50% of the deamination occurred within serotonergic and noradrenergic synaptosomes in the hypothalamic preparation whereas about 80% of the dopamine deamination occurred in the dopaminergic synaptosomes in the striatal preparation. Since these synaptosomes are only a small fraction of the total number of synaptosomes in these preparations a high deaminating rate is due to the accumulation of the amines resulting in high substrate concentration within the aminergic synaptosomes. Because of the irreversible

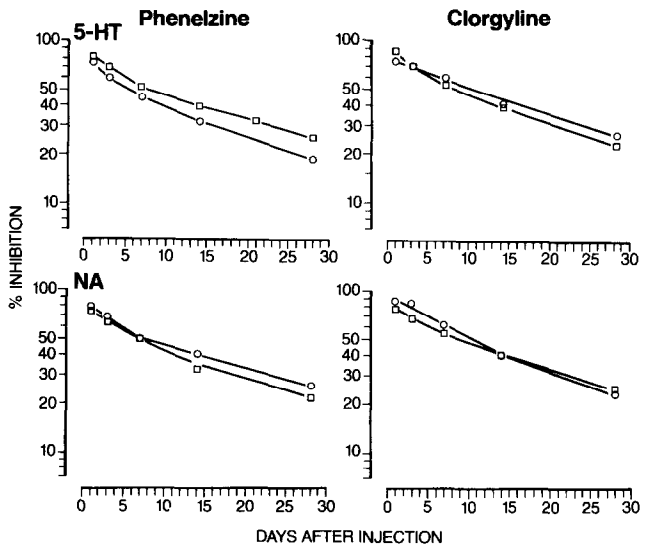


Fig. 5. Duration of the irreversible inhibition of MAO inside (●) and outside (□) serotonergic (5-HT) and noradrenergic (NA) nerve terminals in rat hypothalamus. The rats were injected with phenelzine hydrochloride (4 mg/kg s.c.) and clorgyline hydrochloride (0.5 mg/kg s.c.) at the same occasion and groups of five rats were killed at various times thereafter. The deaminating activities were determined as described in Materials and Methods and the inhibition was calculated in percent of saline-treated rats.

nature of the inhibition the difference in the substrate concentration within the aminergic and the non-aminergic synaptosomes does not influence the degree of inhibition of the amine deamination. However, since the affinity of serotonin for the A-form is much higher than that for the B-form in the rat brain the failure to identify any significant deamination of serotonin by MAO-B does not exclude the possible existence of this form within the serotonergic neurones. Noradrenaline has, on the other hand, a similar affinity for MAO-A and MAO-B in the rat brain [13, 14] but the B form contributes with only about 20% of the total noradrenaline deamination in the rat brain [15]. Our study indicates that the B form within the noradrenaline neurones did not contribute significantly to the deamination of noradrenaline. The same conclusion appears to be valid for the dopamine deamination within dopamine nerve terminals in the rat striatum, although the selegiline experiments indicate that the possibility of about 10% inhibition at low, B-inhibitory doses of selegiline. However, the corresponding clorgyline experiment did not reveal any contribution of the B form of MAO within the dopamine nerve terminals.

A slight contribution of MAO-B to the deamination of all three substrates by the preparations in the presence of the selective uptake inhibitors, e.g. outside these neurones, is indicated by the results obtained with both clorgyline and selegiline. Thus, more than 10% of the deamination was inhibited after treatment with low doses of selegiline. The dose–response curves for the clorgyline inhibition were biphasic. The small (10–20%) second phase appeared at very high doses (>8 mg/kg s.c.) of clorgyline, which may indicate a contribution of the B form to the deamination of the amines. However, another explanation of this second phase may be that at these high doses of clorgyline the compound remains longer in the brain compared with low doses (<1 mg/kg s.c.). The difference may accordingly be due to inhibition of newly synthesized MAO during the 24-hr period between the injection and the death of the rats.

The primary aim of this study was to examine if the irreversibly acting inhibitors have any preference for MAO in the monoamine neurones in the rat brain. This was obviously not the case for the hypothalamic serotonergic and noradrenergic neurones in which the inhibition was less than that outside these neurones. A possible explanation for these findings could be that the transmitter amines partially protected MAO within the nerve terminals against the irreversible MAO inhibition. In favour of this interpretation are the findings that the difference was largest at low doses of the inhibitors. However, the experiments with amine-depleted animals after reserpine pre-treatment did not give any certain support for this hypothesis. Only in two cases (clorgyline and pheniprazine within noradrenergic neurones) did the inhibition reach the same levels inside and outside the aminergic neurones. However, it is possible that the concentrations of free cytoplasmic amines were high enough and increased during the initial reversible phase to partially protect MAO also in the reserpinized animals. Another explanation to the difference in the degree of inhibition outside and inside the amine neurones is that the *in vivo* distribution of the inhibitors may be different, the serotonergic and noradrenergic neurones being less accessible for the inhibitors.

In contrast to the findings in the serotonergic and noradrenergic neurones, the inhibitory actions of the compounds were larger inside than outside the dopaminergic neurones, particularly at higher doses.

The possibility that this preference is due to accumulation of the inhibitors via the membranous dopamine uptake mechanisms was not supported by the experiments in which the dopamine uptake inhibitor amfonelic acid was injected before the two inhibitors phenelzine and tranylcypromine which are structurally most closely related to dopamine. No antagonism was observed.

*d*-Tranylcypromine interferes with several serotonergic mechanisms in the rat brain [13]. The possibility that this compound is transported by the serotonin uptake mechanism was therefore considered. Pretreatment of the rats with the serotonin uptake inhibitor norzimeldine before the injection of *d*-tranylcypromine did not change the degree of the irreversible inhibition of MAO in the serotonergic neurones in hypothalamus. Thus, uptake does not seem to play any significant role for the irreversible MAO inhibitory action of *d*-tranylcypromine in serotonergic neurones in the rat brain.

The deviation from the expected first-order kinetics for the recovery of MAO after inhibition with the irreversible inhibitors may be due to the design of the experiments. The rats were injected with the inhibitors at different times and all rats were killed on the same day. Since the rats were still growing the different weights of the rats may have caused the observed deviation. If so the younger rats should be more sensitive for the inhibitors than the older ones.

In conclusion, the irreversibly acting MAO inhibitors studied showed only small difference in inhibiting MAO inside and outside the monoaminergic neurones in the rat brain. These compounds do not appear to be transported by the specific amine uptake mechanism in the neuronal membranes. However, compounds which have the ability to be transported by the amine pumps and are suicide inhibitors of MAO may be developed. Such compounds could become interesting pharmacological tools and may also have clinical interest.

## REFERENCES


1. D. L. Murphy, N. A. Garrick, C. S. Aulakh and R. M. Cohen, *J. clin. Psychiat.* **45**, 37 (1984).
2. J. A. van der Krogt, E. Koot-Gronsveld and C. J. van den Berg, *Life Sci.* **33**, 615 (1983).
3. A. Stenström, Y. Arai and L. Oreland, *J. Neural Transm.* **61**, 105 (1985).
4. S. B. Ross and A.-L. Ask, *Acta pharmac. tox.* **46**, 270 (1980).
5. A.-L. Ask, I. Fagervall and S. B. Ross, *Naunyn-Schmiedeberg's Archs Pharmac.* **324**, 79 (1983).
6. A.-L. Ask, I. Fagervall and S. B. Ross, in *Monoamine Oxidase and Disease* (Eds. K. F. Tipton, P. Dostert and M. Strolin Benedetti), p. 127. Academic Press, London (1984).
7. J. P. Johnston, *Biochem. Pharmac.* **17**, 1285 (1968).
8. J. Knoll and K. Magyar, *Adv. Biochem. Psychopharmac.* **5**, 393 (1972).
9. R. W. Fuller, B. J. Warren and B. B. Molloy, *Biochem. Pharmac.* **19**, 2934 (1979).
10. S. B. Ross, *Life Sci.* **24**, 159 (1979).
11. J. A. Fuentes, M. A. Oleshansky and N. H. Neff, *Biochem. Pharmac.* **25**, 801 (1976).
12. C. Goridis and N. H. Neff, *J. Neurochem.* **18**, 1673 (1971).
13. H. L. White and A. T. Glassman, *J. Neurochem.* **29**, 987 (1977).
14. N. A. Garrick and D. L. Murphy, *Biochem. Pharmac.* **31**, 4061 (1982).
15. C. J. Fowler and K. F. Tipton, *J. Pharm. Pharmac.* **36**, 111 (1983).
16. D. F. Smith and H. N. Petersen, *Life Sci.* **31**, 2449 (1982).