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EFFECT OF THE ANTIDEPRESSANT MINAPRINE ON BOTH FORMS OF MONOAMINE OXIDASE IN THE RAT

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Abstract—The antidepressant minaprine (3-(2-morpholino-ethylamino) 4-methyl 6-phenyl pyridazine, dihydrochloride) and its main metabolites were examined for their monoamine oxidase (MAO) inhibitory effects in the rat. In our experimental conditions, minaprine displayed *in vitro* a very weak affinity for brain MAO A and B with IC_{50}s close to 1 mM. However, *ex vivo*, after intraperitoneal administration, this drug behaved as a specific and short-acting type A MAO inhibitor (MAOI) of mild potency (ED_{50} = 12.8 mg/kg). In comparison, the reversible type A MAOIs, moclobemide and cimoxatone, were respectively 14 and 5 times more potent. When administered orally, minaprine proved to be considerably less active. The results presented in this study suggest that minaprine inhibits MAO A mainly after being converted into active metabolites. However, the chloroform extractable metabolites were found inactive *in vitro* towards this enzyme, suggesting that MAO inhibitory activity is mediated by one or more other non-identified metabolites.

A number of studies have demonstrated that in most mammalian tissues, monoamine oxidase (MAO, EC 1.4.3.4, monoamine oxygen oxidoreductase (flavin containing)) exists in two distinct forms, i.e. MAO A and MAO B. In the rat brain, type A MAO preferentially deaminates 5-hydroxytryptamine (5-HT, serotonin) and noradrenaline (NA), and is selectively inhibited by clorgyline and harmaline, whereas type B MAO prefers β-phenethylamine (PEA) as substrate and is highly sensitive to the specific inhibitor L-deprenyl. Finally, dopamine (DA) seems to be deaminated by both forms of MAO [1].

During the last few years, selective and short-acting type A MAO inhibitors (MAOIs) have been developed as potential antidepressants since the endogenous monoamines 5-HT and NA are thought to play a major role in depression [2]. These compounds include cimoxatone [3], moclobemide [4], amiflamine [5] and CGP-11305 A [6].

Minaprine [3-(2-morpholino-ethylamino) 4-methyl 6-phenyl pyridazine, dihydrochloride] [7] (Fig. 1) is chemically unrelated to other known psychotropic drugs, and has recently been shown to be effective and well tolerated in the treatment of various depressive disorders [8, 9]. This compound exhibits an original spectrum of antidepressant activities when compared in various rodent models to tricyclic and atypical antidepressants [10]. Moreover, minaprine stimulates central dopaminergic transmission [10–13]. Preliminary biochemical studies have suggested that minaprine administered intraperitoneally could act, at least in part, by inhibiting MAO activity in rat brain [14]. These results prompted us to examine, both *in vitro* and *ex vivo*, the effects of minaprine on MAO A and B activities in the rat. For comparison this study includes two short-acting type A MAOIs, moclobemide (RO 11-1163) and cimoxatone (MD 780515).

MATERIALS AND METHODS

Male Sprague–Dawley albino rats (Charles River Breeding Laboratories, France, 210 ± 20 g, S.E.M.) were used throughout this study. Drugs, dissolved in distilled water or suspended in a filtered solution of gum tragacanth (Merck, 5%, w/v in distilled water), were administered by the intraperitoneal route (i.p.) or orally (p.o.) (5 ml per kg body wt). The doses

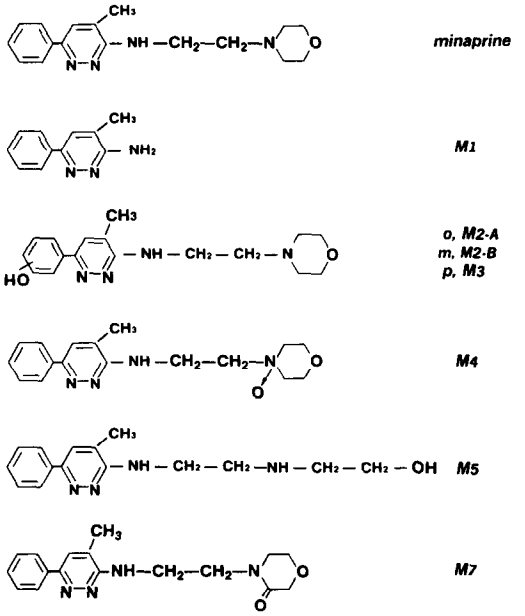

Fig. 1. Structures of minaprine and some of its metabolites (see ref. 17).

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always refer to the salt if any. The rats were decapitated, their striata and liver rapidly dissected out, weighed, frozen on dry ice and stored at −80° until estimation of MAO activity. After thawing, pooled or individual striata (65.2 ± 1.4 mg, S.E.M.) and livers (9.9 ± 0.1 g, S.E.M.) were homogenized in 16 vol. (w/v) of ice-cold 0.1 M Na_2HPO_4/KH_2PO_4 buffer, pH 7.40, using a Polytron homogenizer (PT 10 model, Kinematica, Switzerland; setting 6, 20 sec).

MAO activity was determined according to Kan and Strolin Benedetti [15]. Fifty μl of homogenate were preincubated with the inhibitor (50 μl) in 200 μl of 0.1 M Na/K phosphate buffer, pH 7.4, for 5 min at 37°. When irreversible MAOIs were used, the preincubation time was 30 min. The reaction was started by addition of 50 μl of (^{14}C) 5-HT (MAO A activity) or (^{14}C) PEA (MAO B activity). The final substrate concentrations and incubation times were as follows: 5-HT, striatum and liver, 480 μM and 520 μM respectively, 10 min; PEA, striatum, 12.5 μM, 5 min. Serotonin and PEA concentrations were chosen as 3 times their respective K_m values (Kan, unpublished results). In all cases, enzyme activity was linear with both time and tissue concentration. Finally, in conditions used for determination of MAO A activity in the striatum with 5-HT as substrate, the percentage of the total MAO activity due to the B form did not exceed 3–4% [16]. The reaction was stopped by addition of 250 μl of 2 N HCl and the acid metabolite was extracted in 4 ml of a mixture of toluene–ethylacetate (v/v) by vigorous mixing (Turbula, Bachofen, Switzerland) for 10 min. After centrifugation (1000 *g*, 5 min), 1.5 ml (5-HT) or 1 ml (PEA) of the organic layer were added to 5 ml of the scintillator cocktail Unisolve® (Koch-Light). The radioactivity was measured in a Beckman LS-1801 scintillation spectrometer using plastic mini-vials. Samples run with 2 N HCl were used as blanks. Triplicate determinations at each concentration of the MAOI were used, and 8–12 different concentrations were analysed. The concentrations inhibiting MAO activity by 50% (IC_{50}) were determined from log concentration–inhibition curves. The determination of the kinetic parameters of MAO A (K_m and V_{max}) and the analysis of its inhibition by minaprine, were determined from regression analysis of graphical data (double-reciprocal and Dixon plots). The inhibition of both forms of MAO *ex vivo* after administration of the test compounds to rats was measured *in vitro* as described above. The doses producing 50% inhibition (ED_{50}) were determined from log dose–inhibition plots.

MAO activity was expressed as percent of control ± S.E.M. Statistical significance was calculated using the appropriate tests (see legends of the figures).

Compounds. The following drugs were generously supplied: Cimoxatone (Dr. M. Jalfre, Centre de Recherche Delalande, Rueil Malmaison, France), clorgyline hydrochloride (May & Baker, Dagenham, U.K.) and L-deprenyl hydrochloride (Chinoin, Budapest, Hungary). Minaprine dihydrochloride and harmaline hydrochloride were respectively purchased from Sempa-Chimie (Aramon, France) and Sigma (St Louis, U.S.A.). Moclobemide and β-diethylaminoethyldiphenylpropyl acetate (SKF-525 A) were respectively synthesized by Dr. A. Hallot and Dr. C. Moulineaux (Sanofi Recherches, Montpellier, France). Minaprine metabolites (see ref. 17 and Fig. 1) were synthesized by Pr. C. G. Wermuth (Université Louis Pasteur, Strasbourg, France). 5-Hydroxytryptamine (side chain-2-^{14}C) binoxalate (sp. act. 50 mCi/mmole) and β-phenethylamine (ethyl-1-^{14}C) hydrochloride (sp. act. 48 mCi/mmole) were purchased from New England Nuclear (Boston, U.S.A.).

RESULTS

In homogenates of rat striatum, minaprine behaved as a very weak inhibitor of MAO activity with similar IC_{50} values for MAO A and B ($9\ 10^{-4}$ and $3\ 10^{-3}$ M respectively) (Table 1). Like minaprine, moclobemide slightly inhibited MAO A ($IC_{50} = 6\ 10^{-4}$ M) and MAO B ($IC_{50} = 1\ 10^{-3}$ M). In comparison, cimoxatone was much more potent and specific towards type A MAO ($IC_{50} = 2\ 10^{-8}$ M) (Table 1). As expected, clorgyline and harmaline showed strong affinity and selectivity for MAO A, and L-deprenyl exhibited potent type B MAO inhibiting properties (Table 1). The double-reciprocal plot (Lineweaver–Burk) of MAO A inhibition by minaprine was linear ($r \geq 0.92$). All straight lines crossed on the $1/v$ axis at the same point suggesting that the inhibition was fully competitive in nature (Fig. 2A). In these conditions, the Dixon plot yields a K_i of 174 μM (Fig. 2B). Finally, the minaprine-induced inhibition of MAO A *in vitro* was not modified when the preincubation time was enhanced until 30 min (data not shown).

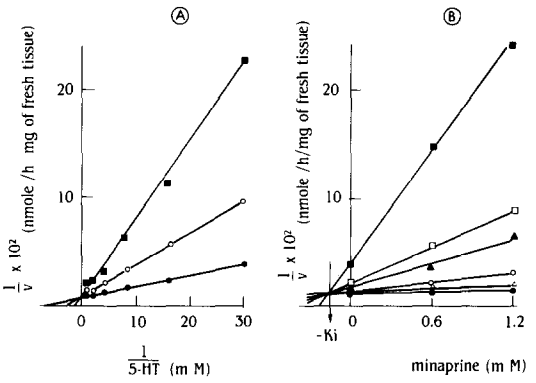

Fig. 2. Effect of minaprine on rat striatal MAO activity using 5-HT as substrate. (A) Double-reciprocal plot of MAO activity vs (^{14}C) 5-HT concentrations. MAO activity was estimated with various concentrations of (^{14}C) 5-HT (0.031, 0.062, 0.125, 0.25, 0.5 and 1 mM) in the absence (●) or in the presence of 0.6 (○) or 1.2 (■) mM of minaprine. Control kinetic constants: K_m = 111 μM; V_{max} = 161 nmoles/hr/mg of fresh tissue. (B) Dixon plot of the inhibition of MAO activity by minaprine. Enzyme activity was estimated with 0.031 (●), 0.062 (△), 0.125 (○), 0.25 (▲), 0.5 (□) and 1 (■) mM of (^{14}C) 5-HT in the presence of two concentrations of minaprine (0.6 and 1.2 mM). K_i = 174 μM.

Table 1. Comparative effects of minaprine and some reference MAOIs on the oxidative deamination of 5-HT and PEA by rat striatum *in vitro*

Compound	MAO inhibition (IC_{50}s, M) 5-HT	PEA	$IC_{50}^{PEA}/IC_{50}^{5\text{-}HT}$
Minaprine	$9 \pm 0.8\ 10^{-4}$	$3 \pm 0.2\ 10^{-3}$	3
Moclobemide	$6\ 10^{-4}$ (5–7)	$1\ 10^{-3}$ (0.9–1.1)	2
Cimoxatone	$2\ 10^{-8}$ (1.8–2.2)	$2\ 10^{-7}$ (1.6–2.4)	10
Clorgyline	$1.6\ 10^{-8}$ (1.5–1.7)	$3.5\ 10^{-6}$ (3–4)	219
Harmaline	$1.8\ 10^{-8}$ (1.3–2.3)	$1.5\ 10^{-4}$ (1.1–1.9)	8333
L-Deprenyl	$1.7\ 10^{-6}$ (1.3–2.1)	$8\ 10^{-9}$ (7–9)	0.005

The values are means derived from 3 (minaprine, mean ± S.E.M.) or 2 (reference MAOIs) experiments carried out with at least 8 drug concentrations each in triplicate. For reference compounds, the values obtained in each experiment are quoted in parenthesis. Control MAO activity (nmole of product/hr/mg of fresh tissue ± S.E.M.), 5-HT: 133 ± 2; PEA: 37 ± 2.

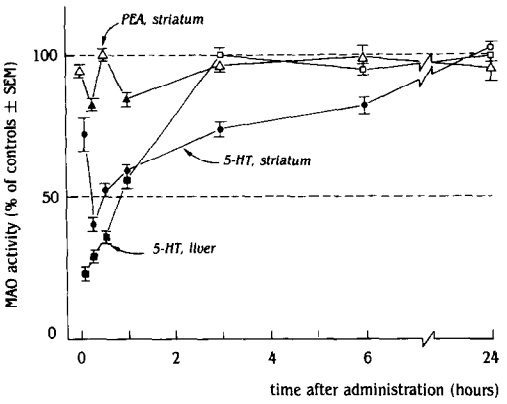

Fig. 3. Time-course of inhibition of type A and B MAO induced by minaprine. Rats (8 per group) received minaprine (20 mg/kg, i.p.) and were sacrificed at different times after treatment. MAO activity was measured in striatum or liver using (^{14}C) 5-HT or (^{14}C) PEA as substrates. The values are expressed as % of controls ± S.E.M. Statistical significance vs control: open symbols, $P > 0.05$; filled symbols, at least $P < 0.05$ (Student's *t*-test). Control MAO activity (nmole/hr/mg of fresh tissue ± S.E.M.), 5-HT, striatum: 160 ± 6, liver: 195 ± 9; PEA, striatum: 44 ± 1.

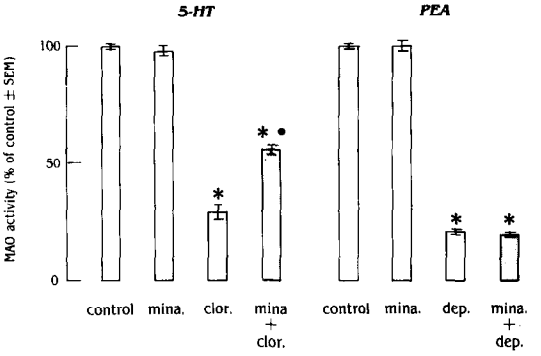

Fig. 4. Effect of minaprine on the long-term inhibition of striatal MAO A and B produced by clorgyline and L-deprenyl respectively. Minaprine (30 mg/kg, i.p.) was injected either alone or 15 min before the irreversible MAOI's (1 mg/kg, i.p.). Rats (8 per group) were sacrificed 24 hr later. Statistical significance (Student's *t*-test): * $P < 0.001$ vs control; ● $P < 0.001$ vs clorgyline. Control MAO activity (nmole/hr/mg of fresh tissue ± S.E.M.), 5-HT: 129 ± 2; PEA: 35 ± 1.

The ED_{50} values determined in homogenates of rat striatum, 15 min or 1 hr after i.p. administration of several MAOIs, are presented in Table 2. *Ex vivo*, minaprine appeared, at least after i.p. administration, as a specific type A MAOI of medium potency ($ED_{50} = 12.8$ mg/kg). In comparison, moclobemide and cimoxatone were respectively 14 and 5 times more potent and preferentially inhibited type A MAO. However, when administered orally, minaprine appeared 10 times less active against MAO A and no significant inhibition of MAO B was observed up to 100 mg/kg (Table 2).

The time-course of inhibition of MAO activity after an acute i.p. administration of minaprine (20 mg/kg) is illustrated in Fig. 3. Using 5-HT as substrate, minaprine clearly inhibited MAO A (maximum inhibition: 77 ± 2% and 60 ± 2% in liver and striatum respectively). These effects peaked respectively at 5 (liver) or 15 min (striatum) post-treatment and declined rapidly thereafter as a function of time, suggesting that the inhibition was reversible in nature. However this reversibility seemed more pronounced in liver than in striatum (Fig. 3). In these experimental conditions, minaprine induced a slight (15–18%) and inconsistent inhibition of MAO B in the striatum (Fig. 3). Finally, a comparable time-course of inhibition was observed in the striatum after oral administration of minaprine (100 mg/kg) (data not shown).

As shown in Fig. 4, the irreversible type A MAOI clorgyline (1 mg/kg, i.p.) induced a 71 ± 2% inhi-

bition of MAO A activity, 24 hr after treatment. In these conditions, enzyme activity was not modified by minaprine (30 mg/kg, i.p.) (Fig. 4). However, when minaprine was injected 15 min prior to clorgyline, a partial protection against this irreversible inhibition was observed, and in these conditions, the clorgyline-induced inhibition was reduced to 44 ± 2% (Fig. 4). Conversely, minaprine did not protect against the irreversible inhibition (79 ± 1%) of MAO B produced by L-deprenyl (1 mg/kg, i.p.) (Fig. 4).

In order to assess if minaprine inhibits MAO A activity *per se* or after conversion into active metabolites, rats were treated with SKF-525 A (75 mg/kg, i.p.) a potent blocker of the hepatic cytochrome P-450 hydroxylating system [18]. Ninety minutes later, an acute dose of minaprine (15 mg/kg) was administered i.p. Animals were sacrificed 15 min after minaprine treatment. In these conditions, the expected reduction of MAO A activity induced by minaprine alone (50 ± 3%) was significantly reduced to 33 ± 2% ($P < 0.001$) in rats pretreated with SKF-525 A. In these conditions, SKF-525 A alone did not inhibit MAO A.

In rats, minaprine undergoes extensive biotransformation and numerous metabolites have been detected [17]. The effect of available chloroform extractable metabolites (Fig. 1) on the oxidative deamination of 5-HT and PEA by rat striatum was studied *in vitro*. As shown in Table 3, none of the compounds tested displayed a significant affinity for either MAO A or MAO B.

DISCUSSION

The results obtained in this study indicate that in our experimental conditions, minaprine, at least *ex vivo* after i.p. administration, behaves as a specific and short-acting type A MAOI. This conclusion is mainly supported by the weak inhibitory effect of minaprine on PEA deamination in striatum, compared to the high inhibition of 5-HT deamination observed in this structure as well as in the liver (Table 2, Fig. 3). Furthermore, no inhibition was observed 24 hr after treatment suggesting that the effect was reversible in nature (Figs. 3 and 4). Thus, the values measured for MAO activity do not represent an absolute determination, but are dependent on the conditions of tissue dilution used in the assay. However, the activity of minaprine after oral administration appeared at doses considerably higher than after i.p. administration (Table 2). Finally, minaprine protected against the irreversible inhibition of MAO A induced by clorgyline thus confirming the reversible and specific effect of the drug towards MAO A (Fig. 4). Similar evidences have been presented with several short-acting type A MAOIs [19] including moclobemide [20] and cimoxatone [15].

According to the *ex vivo* ED_{50} values of MAO A inhibition listed in Table 2, minaprine appeared, as a moderate type A MAOI after i.p. administration. In this respect, minaprine was much less potent than moclobemide and cimoxatone. *Ex vivo*, moclobemide is a very potent, short-acting and selective inhibitor of MAO A (Table 2) [4]. However, *in vitro*, this compound displayed a very slight affinity for this enzyme (Table 1) [21], although much higher IC_{50} values (1–3 μM) have been published [4, 20]. Such discrepancies could be explained, at least in part, by different experimental conditions (tissue dilution, substrate concentrations) used in MAO assays. Biochemical studies have clearly demonstrated that cimoxatone is a potent, specific and reversible type A MAOI [3, 15]. *In vitro*, this compound showed a strong affinity for the active site of MAO A (Table 1) [21, 22]. *Ex vivo*, cimoxatone was, however, less potent than expected (Table 2) due to its biotransformation to a less active metabolite [22].

The discrepancy between *in vitro* and *ex vivo* (i.p. or p.o.) results with minaprine (Tables 2 and 3) suggests that one (or several) metabolite(s) may be responsible for MAO A inhibition. This conclusion could be supported by the following observations. Brain concentrations of unchanged minaprine (12–14 μM) detected in rat after an acute i.p. dose of 15 mg/kg [23] were 10 times below its K_i value towards brain MAO A (174 μM, Fig. 1). Furthermore, when the hepatic microsomal cytochrome P-450 hydroxylating system was blocked by SKF-525 A [18], a slight but significant decrease of the mina-

Table 2. Comparative effects of minaprine and two reference type A MAOIs moclobemide and cimoxatone, on the oxidative deamination of 5-HT and PEA by rat striatum *ex vivo*

Compound		MAO inhibition (ED_{50}s, mg/kg)	
		5-HT	PEA
Minaprine	i.p.	12.8 (10.4–15.9)*	>30 (4%)†
	p.o.	95.2 (57.7–150)	>100 (3%)
Moclobemide	i.p.	0.9 (0.6–1.4)	100 (48%)
Cimoxatone	i.p.	2.8 (2.4–3.3)	54.8 (50.7–59.3)

Drugs were injected i.p. or p.o. to rats, 15 min (minaprine) or 1 hr (moclobemide and cimoxatone) before decapitation and striatal MAO activity estimated with either (^{14}C) 5-HT or (^{14}C) PEA as substrates. Values are means derived from two experiments carried out with 4–5 drug doses (6 rats each).

* 95% confidence limits.

† % inhibition at this dose. Control MAO activity (nmole/hr/mg of fresh tissue ± S.E.M.), 5-HT: 191 ± 5; PEA: 37 ± 1.

prine-induced inhibition of brain MAO A was observed. However, the effect of SKF-525 A was rather weak (17%) suggesting that part of the conversion of minaprine could not involve this system.

Minaprine undergoes extensive biotransformation in different species including rat, with major groups of metabolites derived from phenyl-hydroxylation or degradation of the morpholin ring [17]. The difference in potency towards MAO A between the i.p. and the p.o. route cannot be ascribed to a poor biodisponibility since in rats 90% of minaprine is absorbed after oral administration. This difference could be due to metabolic differences between the two routes although no qualitative or quantitative differences were observed in the chloroform extractable metabolites after i.p. or oral administration.* These metabolites were tested, but brain type A MAO was not inhibited by any of the compounds tested (Table 3). In particular, metabolites M_3 and M_5 (Fig. 1), which were detected in rat and monkey brain after minaprine administration * [23, 24], were inactive (Table 3). Thus the precise mechanism by which minaprine inhibits type A MAO *ex vivo*, is at present unclear. However, the existence of an undetected metabolite with sufficient affinity for this enzyme cannot be excluded.

As far as monoamine levels and metabolism are concerned, minaprine was reported to induce modifications which are compatible with MAO inhibition. Thus, minaprine (3–30 mg/kg, i.p.) enhanced 5-HT levels in various rat brain regions. This increase was associated with a significant reduction of 5-hydroxyindolacetic acid (5-HIAA) levels [25, 26]. In these conditions, minaprine failed to modify striatal DA levels, but decreased its acid metabolites 3–4 dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA), and enhanced the levels of 3-methoxytyramine (3-MT), the extraneuronal metabolite of DA [14]. In terms of dose-ranging and time dependency, these effects are consistent with the minaprine-induced MAO A inhibition, reported above. Comparable patterns have been published for moclobemide [4, 20] and cimoxatone [3].

Similarly, part of the pharmacological profile of minaprine in rodent models of antidepressant activity fits with its MAO inhibiting properties. Thus, like most type A MAOIs [27], minaprine antagonized the effects of reserpine, potentiated 5-hydroxytryptophan (5-HTP)-induced tremor and head-twitches, and reduced immobility in the despair test, in mice, with a dose-range of 3 to 30 mg/kg i.p. and p.o. [10]. This suggests that the MAO inhibitory effect of minaprine does not fully account for its pharmacological activities.

This study clearly indicates that *ex vivo*, at least after i.p. administration, in rodents the antidepressant drug minaprine behaves, as a moderate specific and short-acting type A MAOI. This property appears to be mediated by (a) yet non-identified metabolite(s).

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* Caccia *et al.*, personal communication.

Table 3. Comparative effects of some metabolites of minaprine on the oxidative deamination of 5-HT and PEA by rat striatum *in vitro*

Metabolite	MAO inhibition (IC_{50}s, M)	
	5-HT	PEA
M_1	$2.3\ 10^{-4}$	$> 10^{-3}$ (31%)
$M_{2\text{-}A}$	$> 10^{-3}$ (33%)*	$1\ 10^{-3}$
$M_{2\text{-}B}$	$> 10^{-4}$ (0%)	$> 10^{-4}$ (1%)
M_3	$> 10^{-3}$ (14%)	$>10^{-3}$ (0%)
M_4	$> 10^{-3}$ (2%)	$> 10^{-3}$ (5%)
M_5	$7\ 10^{-4}$	$> 10^{-3}$
M_7	$6.4\ 10^{-4}$	$7.4\ 10^{-4}$

See Fig. 1 and legend of Table 1. Control MAO activity (nmole of product/hr/mg of fresh tissue ± S.E.M.); 5-HT: 152 ± 9; PEA: 38 ± 2.

* % inhibition at this concentration.

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