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Interactions of tricyclic antidepressant drugs with human and rat monoamine oxidase type B

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Summary. The effect of tricyclic antidepressant drugs on the deamination of phenylethylamine and benzylamine by monoamine oxidase (MAO) type B was investigated in vitro in human brain cortex, human platelet, and rat brain preparations. These drugs inhibited MAO activity as expected; however, an atypical biphasic response was observed with the tertiary amine tricyclic, clomipramine, and, to a somewhat lesser extent, with two other tertiary amine tricyclics, imipramine and amitriptyline, when benzylamine was used as the substrate in human tissue preparations. This atypical biphasic pattern was not found when we used the secondary amine antidepressant drugs, desipramine, desmethylclomipramine, or fluoxetine, or used phenylethylamine as the substrate, or used rat rather than human brain tissue. For the tricyclics exhibiting normal inhibition patterns, the same rank order of inhibition was observed with benzylamine as a substrate in all three types of tissue; however with phenylethylamine, differences in inhibition were found between rat and human tissues. These tricyclic-MAO interactional data suggest that secondary and tertiary amine tricyclics interact differently with human MAO type B, that rat and human MAO type B are not functionally identical, and also support other data that phenylethylamine and benzylamine are deaminated by different mechanisms.

Key words: Monoamine oxidase type B – Tricyclic antidepressive agents – Phenylethylamine – Benzylamine – Human platelets and brain cortex – Rat brain

Introduction

In addition to their prominent effects as inhibitors of norepinephrine and serotonin reuptake into nerve terminals (Glowinski and Axelrod 1966; Carlsson et al. 1968, 1969), tricyclic antidepressant drugs acts as weak reversible inhibitors of the enzyme, monoamine oxidase (MAO) (Edwards and Burns 1974; Roth 1976a, b, 1978, 1979), with more potent inhibitory actions on the MAO type B isozyme than type A (Roth 1976a). Phenylethylamine and benzylamine, two MAO type B selective substrates, exhibit different kinetic interactions with the tricyclic antidepressant drugs; phenylethylamine is inhibited noncompetitively while benzylamine is inhibited competitively (Edwards and Burns 1974; Roth 1976b, 1979), suggesting the presence of isozymes of MAO type B or multiple catalytic sites on MAO type B (Edwards and Burns 1974). Other evidence that supports this hypothesis are the different Arrhenius plots observed for the deamination of phenylethylamine and benzylamine (Kobayashi et al. 1979), the activation of human platelet MAO by a plasma factor when benzylamine but not phenylethylamine was used as the substrate (Yu and Boulton 1979), and the noncompetitive inhibition patterns found with phenylethylamine and benzylamine in mixed substrate analyses (Edwards and Chang 1975; Roth 1976b). On the other hand, steady state methods (Pearce and Roth 1985) and other mixed substrate analyses, which have reported competitive inhibition patterns with phenylethylamine and benzylamine (Roth 1976b; Fowler et al. 1979), suggest that the deamination of the two substrates occurs at a single catalytic site. Furthermore, similar results were obtained for the deamination of phenylethylamine and benzylamine under the following three conditions: inhibition of MAO by J-508, an analog of the selective MAO type B inhibitor, deprenyl (Fowler et al. 1980); thermal denaturation of MAO at 50° C; and inactivation of MAO by extraction of lipids with 2-butanone (Fowler et al. 1979). In view of these results, further evaluation of the mechanisms of phenylethylamine and benzylamine deamination by MAO type B is warranted.

Another issue that requires further examination is the characterization of MAO activity across species and tissues. The presence of various proportions of the MAO type A and B isozymes across species and tissues has been well documented. For example, rat brain has about equal amounts of type A (55%) and B (45%) activity (Johnston 1968; Hall et al. 1969; Squires 1972; Houslay and Tipton 1976; Garrick et al. 1979), while human brain has predominantly type B (70%) activity (Garrick et al. 1979), and human platelets have only the type B isozyme (Donnelly and Murphy 1977). In addition, species differences in the structure of MAO type B probably exist since immunologic studies have reported that a monoclonal antibody to human platelet MAO type B immunoprecipitated MAO type B from human tissues but not from rat liver (Denney et al. 1982, 1983; Denney and Denney 1985). Future studies are necessary to determine whether these structural differences between species also correspond to functional differences.

In the present study, we used the effects of tricyclic antidepressant drugs on MAO type B activity to evaluate further possible differences in the deamination of benzylamine and phenylethylamine and to characterize more completely some features of MAO type B activity in human and rat tissues.

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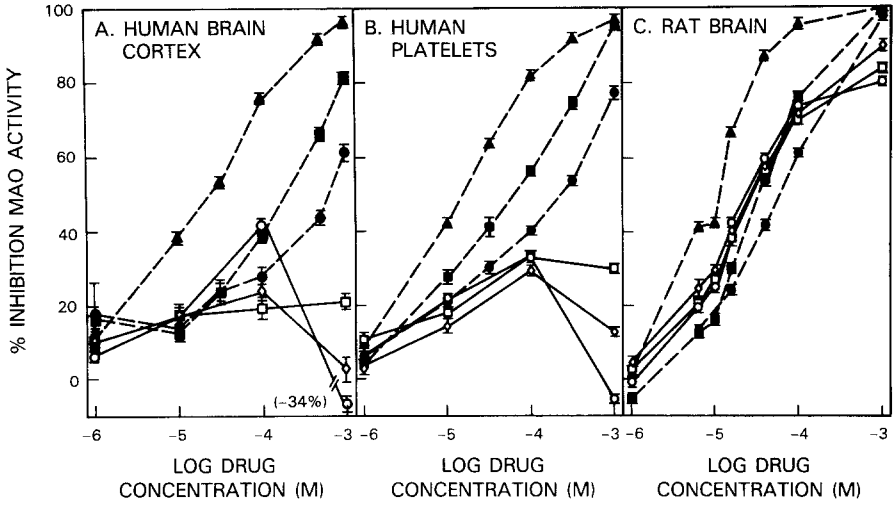

Fig. 1. Tricyclic antidepressant drug inhibition of MAO activity in human brain cortex (**A**), human platelets (**B**), and rat brain (**C**). Benzylamine (80 μM) was used as the substrate. Drugs analyzed included fluoxetine (▲----▲), desmethylclomipramine (■----■), desipramine (●----●), amitriptyline (□——□), imipramine (◇——◇), and clomipramine (○——○). *Each point* represents the mean ± SEM of duplicate determinations on three separate occasions

Methods

Enzyme preparation. Whole brains from Sprague-Dawley male rats (Taconic Farms, Germantown, NY, USA) were homogenized in 10% (w/v) 0.08 M phosphate buffer (Na_2HPO_4-KH_2PO_4), pH 7.2. The homogenate was centrifuged at $900 \times g$ for 10 min at 4° C. The supernatant was removed, sonicated for 15 s (Sonifer Cell Disruptor, Heat Systems-Ultrasonics, Inc., Plainview, LI, NY, USA), and then stored at −80° C until assayed. Human brain cortical tissue was obtained at autopsy within 30 h of death. This tissue was prepared for analysis as described above. Human platelet-rich plasma collected with acid citrate dextrose (ACD) solution as the anticoagulant (NIH Blood Bank) was centrifuged at $2000 \times g$ for 20 min to yield platelet pellets. The pellets were washed with cold saline, resuspended with distilled water, sonicated for 15 s, and then stored at −80° C.

MAO activity assay. MAO activity using the substrates, benzylamine (Murphy et al. 1976) and phenylethylamine (Garrick and Murphy 1982), was determined as previously described except that the analyses were executed with 80 μM ^{14}C-benzylamine and 1.5 μM ^{14}C-phenylethylamine. Soluble amine oxidase, another enzyme that uses benzylamine as a substrate, was simultaneously determined with MAO (Murphy et al. 1976). Protein was determined by a modified method of Lowry et al. (1951) using bovine serum albumin as the standard.

Inhibition studies. The antidepressant drugs, clomipramine (Ciba-Geigy, Summit, NJ, USA), desmethylclomipramine (Ciba-Geigy Ltd., Basel, Switzerland), fluoxetine (Eli Lilly and Co., Indianapolis, IN, USA), amitriptyline, imipramine, and desipramine (Sigma Chemical Co., St. Louis, MO, USA) were used for the inhibition studies. These drugs were incubated with the enzyme preparation at concentrations between 10^{-3} M to 10^{-6} M for 15 min at 37° C prior to adding radioactive substrates so that the drugs equilibrated with MAO. In an additional benzylamine study, we incubated the rat brain preparation with clorgyline (10^{-7} M) for 15 min at 37° C to inhibit MAO type A (Garrick and Murphy 1982) prior to the addition of the antidepressant drugs. The effect of tertiary amine tricyclic antidepressant drugs on benzylamine deamination by rat brain MAO was also re-evaluated after the enzyme was diluted 14- and 42-fold.

Mean pI_{50} values (negative logarithms of the inhibitor concentration that produced 50% inhibition of MAO activity) were determined for each drug using a regression analysis. Only concentrations of the drug between 10^{-3} M to 10^{-6} M were used in the calculations because these values represented the linear portion of the curves. Analysis of variance accompanied by post hoc *t*-tests were used to determine statistical significance for differences among drug effects. The calculations utilized the Statistical Analysis System (SAS Institute, Cary, NC, USA).

Kinetic constant determinations. Apparent Michaelis constant (K_m) and maximum velocity (V_{max}) values were determined from Hanes transformations (substrate vs. substrate/velocity) of the Michaelis-Menten equation. Six substrate concentrations between 4 to 200 μM were used for benzylamine determinations and 0.15 to 25 μM for phenylethylamine determinations.

Results

Inhibition of benzylamine deamination

Human brain cortex and human platelet. The tricyclic antidepressant drugs exhibited normal inhibition of MAO activity, with the exception of the tertiary amine tricyclic antidepressant drugs, clomipramine, amitriptyline, and imipramine, in human brain cortex (Fig. 1 a) and human platelets (Fig. 1 b). An activation of MAO activity occurred with 10^{-3} M clomipramine in human cortex, while an atypical biphasic response occurred with clomipramine in human platelets and with imipramine in both human platelet and brain preparations. The percentage of inhibited MAO activity with amitriptyline levelled off at 10^{-4} M in human platelets and at 10^{-5} M in human cortex. This effect could not be explained by the presence of soluble amine oxidase, another enzyme that uses benzylamine as a substrate, because the enzyme was not found in our human platelet preparations (data not shown), and only negligible amounts (3.4 ± 0.3% of total benzylamine deamination; mean ± SEM, $n = 4$) were found in human brain cortex. The secondary amine tricyclic antidepressant drugs, desmethylclomipramine or

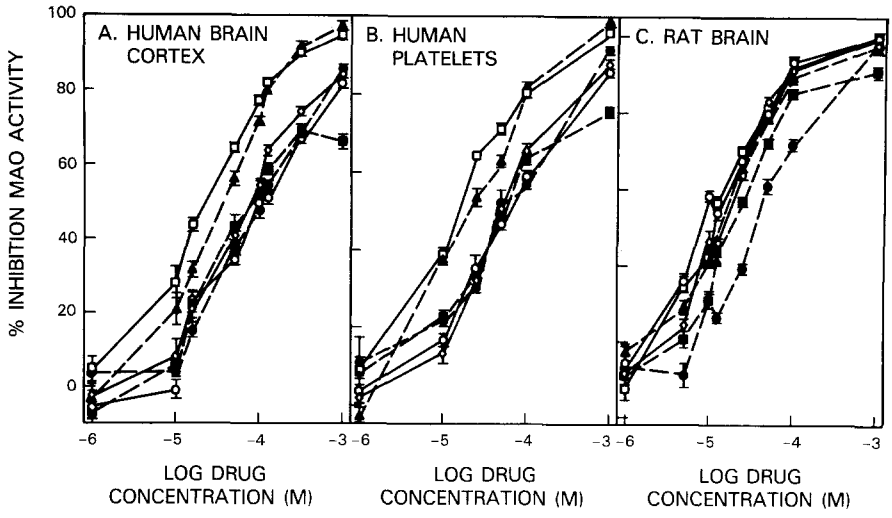

Fig. 2. Tricyclic antidepressant drug inhibition of MAO activity in human brain cortex (**A**), human platelets (**B**), and rat brain (**C**). Phenylethylamine (1.5 μM) was used as the substrate. Drugs analyzed included fluoxetine (▲----▲), desmethylclomipramine (■----■), desipramine (●----●), amitriptyline (□——□), imipramine (◇——◇), and clomipramine (○——○). *Each point* represents the mean ± SEM of triplicate determinations on three separate occasions

Table 1. pI_{50} Values for tricyclic antidepressant drug inhibition of benzylamine deamination by MAO in human brain cortex, human platelets, and rat brain*

	Benzylamine pI_{50} (M)		
	Human cortex	Human platelets	Rat brain
*Secondary amine drugs***, ****			
Desipramine	3.17 ± 0.16***	3.67 ± 0.06***	4.20 ± 0.03***
Desmethylclomipramine	3.77 ± 0.08***	4.25 ± 0.06***	4.46 ± 0.02
Fluoxetine	4.69 ± 0.06***	4.84 ± 0.02***	5.01 ± 0.05***
Tertiary amine drugs			
Clomipramine	>3	>3	4.62 ± 0.09
Imipramine	>3	>3	4.55 ± 0.02
Amitriptyline	>3	>3	4.49 ± 0.03

* pI_{50} is the negative logarithm of the inhibitor concentration which produced 50% inhibition of benzylamine deamination by MAO. Values are means ± SEM

** Each drug exhibited the following potency of inhibition with the tissue preparations: rat brain > human platelets > human cortex ($p < 0.05$), except fluoxetine in human platelets which was not different from either human cortex or rat brain

*** Significantly different from each of the other drugs within a given tissue ($p < 0.01$)

**** The secondary amine drugs in rat brain were significantly different from each other ($p < 0.02$)

desipramine, or the secondary amine bicyclic antidepressant, fluoxetine, did not produce the atypical biphasic response with MAO.

Of the secondary amine drugs exhibiting normal inhibition patterns, fluoxetine was the most potent inhibitor followed by desmethylclomipramine and then desipramine ($p < 0.01$ for differences among drugs, Table 1). In addition, desmethylclomipramine and desipramine produced greater inhibition of human platelet MAO than human cortex MAO ($p < 0.05$), while fluoxetine inhibited both human platelet and brain preparations similarly (Table 1).

Rat brain. All the tricyclic antidepressant drugs exhibited normal inhibition patterns with rat brain MAO (Fig. 1c). Fluoxetine was the most potent inhibitor and desipramine was the least potent inhibitor ($p < 0.01$), while the other drugs with intermediate potencies all produced similar amounts of inhibition (Table 1).

Comparison of human and rat tissues. All the secondary amine antidepressant drugs except fluoxetine, which inhibited rat brain and human platelet MAO similarly (Table 1), inhibited rat brain MAO more than either human platelet or brain MAO ($p < 0.05$). As with the human enzyme preparations, we noted the same rank order of inhibition with the secondary amine drugs (fluoxetine > desmethylclomipramine > desipramine) with rat brain MAO ($p < 0.02$, Table 1). The atypical biphasic response, which was seen with the human tissues with the tertiary amine tricyclics, was not found in the rat brain tissue (Fig. 1). This effect was probably not caused by the deamination of benzylamine by MAO type A, since incubating rat brain preparations with 10^{-7} M clorgyline, a MAO type A selective inhibitor, did not alter the effect of the tricyclics (data not shown).

Inhibition of phenylethylamine deamination

Human brain cortex and human platelet. The tricyclic antidepressant drugs inhibited MAO type B in human brain cortex (Fig. 2a) and human platelets (Fig. 2b) as expected. Each drug was a more potent inhibitor of human platelet than human cortex preparations ($p < 0.05$, Table 2). Fluoxetine and amitriptyline, which produced similar results, inhibited human platelet MAO to a greater extent ($p < 0.01$) than the other drugs which responded similarly (Table 2). The same effect was also seen with human cortex MAO, except that amitriptyline was a more potent inhibitor than fluoxetine ($p < 0.01$, Table 2).

Rat brain. The inhibition of MAO by tricyclic antidepressant drugs in rat brain is depicted in Fig. 2c. Clomipramine, amitriptyline, imipramine, and fluoxetine all inhibited MAO similarly; clomipramine and amitriptyline were more potent inhibitors than desmethylclomipramine ($p < 0.01$, Table 2). Desipramine was the least potent inhibitor ($p < 0.01$, Table 2).

Comparison of human and rat tissues. The antidepressant drugs inhibited rat brain MAO to a greater extent than either human platelet or brain MAO ($p < 0.05$, Table 2). The same

Table 2. pI_{50} Values for tricyclic antidepressant drug inhibition of phenylethylamine deamination by MAO in human brain cortex, human platelets, and rat brain

	Phenylethylamine pI_{50} (M)*		
	Human cortex	Human platelets	Rat brain
Secondary amine drugs			
Desipramine	3.96 ± 0.03	4.21 ± 0.07	4.46 ± 0.01 **
Desmethyl-clomipramine	4.07 ± 0.05	4.29 ± 0.04	4.72 ± 0.01
Fluoxetine	4.43 ± 0.05 **	4.70 ± 0.04 ***	4.85 ± 0.02
Tertiary amine drugs			
Clomipramine	3.94 ± 0.06	4.21 ± 0.03	5.05 ± 0.07 ****
Imipramine	4.11 ± 0.05	4.30 ± 0.03	4.87 ± 0.05
Amitriptyline	4.65 ± 0.07 **	4.78 ± 0.01 ***	4.96 ± 0.06 ****

* Each drug exhibited the following potency of inhibition in the tissue preparations: rat brain > human platelets > human cortex ($p < 0.05$)
** Significantly different from each of the other drugs within a given tissue ($p < 0.01$)
*** Amitriptyline and fluoxetine were not different from each other but were significantly different from each of the other drugs in human platelets ($p < 0.01$)
**** Significantly different from desmethylclomipramine in rat brain ($p < 0.01$)

Table 3. Kinetic constants for MAO deamination of benzylamine and phenylethylamine in human brain cortex, human platelets, and rat brain*

Tissue	Apparent K_m (μM)		V_{max} (nmoles/mg protein/h)	
	Phenyl-ethylamine	Benzyl-amine	Phenyl-ethylamine	Benzyl-amine
Human brain cortex	2.1 ± 0.2	18.1 ± 3.5	15 ± 2	43 ± 1
Human platelets	1.9 ± 0.4	10.5 ± 1.5	16 ± 2	54 ± 2
Rat brain	5.0 ± 0.2	20.0 ± 1.0	23 ± 3	78 ± 1

* Values are means ± SEM

rank order of inhibition observed among the drugs in the human tissues was not found in the rat brain (Table 2).

Comparison of inhibition of benzylamine and phenylethylamine deamination

The atypical biphasic response, which occurred in the human tissue preparations with benzylamine, was not found in any of the enzyme preparations when phenylethylamine was used as the substrate (Figs. 1 and 2).

Kinetic constant determinations. The apparent K_m and V_{max} values for MAO deamination of benzylamine and phenylethylamine are reported in Table 3. In general, similar apparent K_m values were obtained with the different enzyme preparations for each substrate. With phenylethylamine, the V_{max} values were similar among the MAO preparations, but with benzylamine, the V_{max} values decreased with the following rank order: rat brain > human platelet > human cortex. To determine whether the higher MAO V_{max} in rat brain (indicating increased enzyme concentration) explains the lack of atypical biphasic response with benzylamine deamination by the tertiary amine tricyclics, we measured MAO activity after rat brain preparations were diluted 14- and 42-fold. Similar percentages of inhibition were obtained for the tertiary amine tricyclics with each enzyme concentration (data not shown). To evaluate whether the different responses of benzylamine and phenylethylamine to the tricyclics in human brain and platelet tissues could be attributed to a slightly higher concentration of benzylamine (relative to its K_m), we repeated the clomipramine experiments with the human tissues using 10 μM benzylamine. Similar atypical biphasic responses were again observed, with maximum inhibition found with 10^{-4} M clomipramine, and substantially less inhibition with 5×10^{-4} and 10^{-3} M clomipramine (data not shown).

Discussion

The tricyclic antidepressant drugs inhibited MAO activity in our study as other studies have previously reported (Edwards and Burns 1974; Roth 1976a, b, 1978, 1979). In our analysis, however, we included two drugs, desmethylclomipramine, a metabolite of clomipramine, and fluoxetine, a bicyclic antidepressant, which had not previously been evaluated. In our study, the tertiary amine antidepressant drugs, especially clomipramine, interacted with MAO type B differently than the secondary amine drugs, in that the tertiary amine drugs exhibited an atypical biphasic response with benzylamine in the human tissues. In other studies, tertiary amine tricyclics have been reported to inhibit serotonin reuptake more potently than their corresponding secondary amine metabolites, while the opposite has been reported for the norepinephrine reuptake system (Carlsson et al. 1969; Shaskan and Snyder 1970; Benfield et al. 1980). Clinically, tertiary amine tricyclics are more potent than secondary amine tricyclics in causing sedation, anticholinergic effects, cardiotoxicity, orthostatic hypotension, weight gain, and cognitive impairment (Preskorn 1986). These effects might result from the tertiary tricyclics' properties as differential inhibitors of reuptake and/or MAO activity. Another tertiary-secondary tricyclic difference – the depression of firing rates of rat brain raphe neurons by tertiary but not by secondary amine tricyclic drugs (Sheard et al. 1972) – is not likely to be MAO-inhibition related, since we found no tertiary-secondary drug differences in the deamination of either substrate in rat brain.

Our study also indicates that human tissue MAO type B is not functionally identical to rat brain MAO type B in its deamination of benzylamine and phenylethylamine in the presence of tricyclic drugs. In our study, similar results were obtained with the two MAO type B substrates, benzylamine and phenylethylamine, in both human cortex and platelet preparations, as previously reported for other characteristics of MAO type B (Denney et al. 1983; Young et al. 1986). In contrast, different interactions were found with rat brain MAO type B. Most notably, the tertiary amine tricyclics did not produce the atypical biphasic response in rat brain with benzylamine that was found in the human tissues. The characteristic atypical biphasic response was not produced

in rat brain even when MAO type A was inhibited by clorgyline or when the enzyme preparation was diluted. Furthermore, the substrate, phenylethylamine, which had normal patterns of inhibition, yielded the same rank order of inhibition among the tricyclics in human tissues, while in rat brain a different inhibitory relationship was observed. These differences between species are supported by immunologic data which showed that a monoclonal antibody to platelet MAO type B recognized human cortex and platelet MAO type B as the same (Denney et al. 1983) but did not recognize rat liver MAO type B (Denney and Denney 1985). These functional and immunologic data demonstrate that it may not be possible to extrapolate results from rodent MAO type B studies to human tissues.

Furthermore, our study suggests that human platelet and brain cortex contain either multiple catalytic sites or isozymes of MAO type B for the deamination of phenylethylamine vs. benzylamine as previously proposed by others (Edwards and Burns 1974; Kobayashi et al. 1979). We base this hypothesis on the finding that tertiary amine tricyclic antidepressant drugs produced an atypical biphasic response in human enzyme preparations with benzylamine but not with phenylethylamine as the substrate. This effect has not been previously reported. In a prior study, human platelet MAO was inhibited sigmoidally by amitriptyline or imipramine with benzylamine as the substrate (Edwards and Burns 1974); however, in this study, the platelet preparation was sonicated for 2 h with 10^{-3} M benzylamine and 1% (v/v) Triton X-100, a major methodologic difference that may have contributed to these discrepant results. In other studies with human cortex MAO, high concentrations of amitriptyline (Roth 1976b) or imipramine (Roth 1979) were not studied. The human tissue response that we report was not caused by a nonspecific effect such as interaction of the tricyclics with benzylamine because the atypical biphasic response was not reproduced in rat brain. Soluble amine oxidase, another enzyme that uses benzylamine as a substrate, is also not responsible for the MAO response differences because this enzyme was not found in our human platelet preparation and only negligible amounts were found in our human cortex preparation. In view of these results, caution is recommended when comparing MAO type B data obtained from human vs. rodent species and from laboratory analyses using the substrates benzylamine vs. phenylethylamine.

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