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Platelet monoamine oxidase B: Use and misuse

by M. B. H. Youdim

Rappaport Family Research Institute, and Department of Pharmacology, Faculty of Medicine, Technion, Haifa (Israel)

Summary. The human platelet in addition to having serotonin (5-HT) receptors, uptake carriers (receptor) and transmitter storage vesicles, primarily possesses mitochondrial monoamine oxidase (MAO) type B. Similar to the major form of MAO in the human brain, this enzyme actively oxidizes A-B and B substrates (tyramine, dopamine, phenylethylamine) as well as the novel secondary amine anticonvulsant, milacemide and dopaminergic neurotoxin, MPTP. 5-HT oxidation is hardly affected by the platelet enzyme and MAO inhibitors have no net effect on its accumulation. MAO-B is selectively inhibited by 1-deprenyl and thus the platelet enzyme may be useful to monitor the anti-Parkinson activity of such drugs, as related to their ability to inhibit brain MAO-B. The oxidation of the anticonvulsant, milacemide, to glycine in vitro and in vivo by MAO-B, may herald new prospects for the development of inert prodrugs capable of being metabolized to neuroactive substances by MAO-B. The plasma levels of their metabolites may be an index of MAO-B activity found in the platelet and brain.

Key words. Monoamine oxidase A and B; serotonin; phenylethylamine; milacemide; Parkinson's disease; epilepsy; anticonvulsant; platelet; clorgyline and deprenyl.

Introduction

The human platelet has proved to be an attractive, but limited, model of central serotonin (5-HT) neurones, because it possesses LSD and 5-HT receptors, 5-HT uptake transporter (imipramine binding sites)[21, 32, 34] and mitochondrial monoamine oxidase (MAO) B[19, 62, 65, 68]. However, unlike the 5-HT neurones it cannot synthesize the neurotransmitter since it lacks the rate-limiting enzyme, tryptophan hydroxylase[24]. Nevertheless, the platelet has been a useful organelle for the study of basic and clinical actions of psychotropic drugs[34, 44, 45]. The purpose of this paper is not to review the available literature on platelet monoamine oxidation in normal and pathological conditions, but to point out the use and misuse of it. For an extensive analysis of platelet MAO activity in psychiatric disorders, refer to a recent review by Fowler et al.[19].

Basic biochemistry of MAO

The outer mitochondrial membrane bound flavoprotein enzyme, MAO, catalyzes the oxidative deamination of a variety of primary amines including 5-HT, dopamine, noradrenaline, octopamine, tryptamine and phenylethylamine (table 1). This primary amine inactivating function of MAO gives the enzyme an important regulatory role within the aminergic neurones[30, 31, 62–64]. However, more recent observations clearly illustrated that the enzyme may have other functions unrelated to its ability of inactivating amine neurotransmitter substances in the CNS. Thus it can oxidize rather inert amines such as (a) MPTP (N-methyl-6-phenyl-1,2,3,6-tetrahydropyridine) to the selective dopaminergic Parkinson-inducing neurotoxin MPP^+ (N-methyl-6-phenylpridinium ion)[25, 36, 37] or (b) the novel anticonvulsant, milacemide (2-*n*-pentylaminoacetamide), to the inhibitory neurotransmitter, glycine[58, 72]. Therefore, MAO-B is endowed with properties which include amine detoxification as well as promotion of neurotoxin and neurotransmitter formation (table 1).

Table 1. Substrates and inhibitors of MAO-A and MAO-B

	MAO-A	MAO-B
Substrates		
Noradrenaline	+	
Adrenaline	+	
Serotonin	+	
Octopamine	+	
5-methoxytryptamine		+
Benzylamine		+
Phenylethylamine		+
p-methoxyphenylethylamine		+
MPTP		+
Milacemide		+
Dopamine	+	+
Tyramine	+	+
Inhibitors		
Clorgyline	+	
LY 51461	+	
Moclobamide	+	
Deprenyl		+
AGN 1135		+
MDL-72145		+
RO 16-6491		+
Milacemide		+
Tranylcypramine	+	+
Phenelzine	+	+

Taken from references 1, 25, 27, 37, 50, 55, 56, 58, 68, 70.

MAO exists as two catalytically active forms termed MAO-A and MAO-B[26]. The former is sensitive to inhibition by low concentration of the irreversible suicide acetylenic inhibitor clorgyline and the B form sensitive to inhibition by other acetylenic derivatives, 1-deprenyl[28] and AGN 1135[55, 64, 68]. The substrate and inhibitors of the two forms are presented in table 1. Distribution of MAO-A and MAO-B varies significantly in rat and human tis-

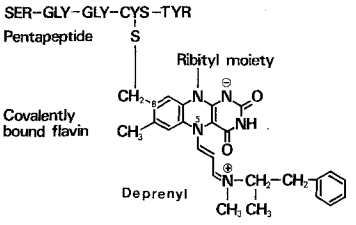

Figure 1. The structure of the cysteinyl-flavin at the active center of MAO-B and the adduct formed when the enzyme is inactivated irreversibly by 1-deprenyl[27, 53, 59].

Table 2. The relative substrate specificity of mitochondrial MAO-B prepared from various sources. The human brain MAO was prepared from caudate nucleus and the residual MAO-A activity was inhibited by preincubation for 60 min with clorgyline (0.1 μM). (Youdim, unpublished data).

Substrate	Relative rate (%) Type	Platelet	Human brain	Beef liver
Benzylamine	B	100	100	100
Tyramine	A and B	105	110	85
Tryptamine	B	–	–	45
2-Phenylethylamine	B	51	52	45
Dopamine	A and B	48	54	44
5-Hydroxytryptamine	A	16	14	19
Epinephrine	A	14	12	9
Norepinephrine	A	–	–	4
Milacemide	B	30	37	27
MPTP	B	35	39	41

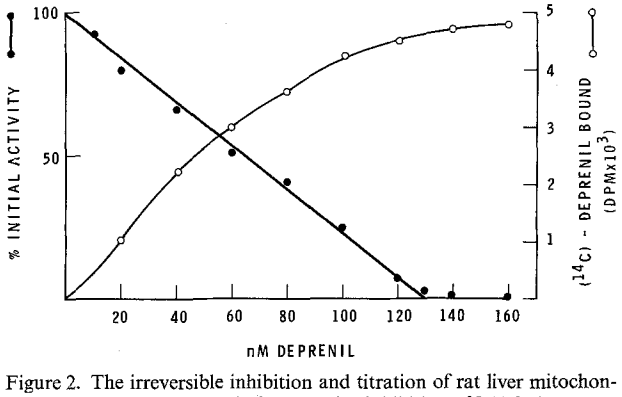

Figure 2. The irreversible inhibition and titration of rat liver mitochondrial MAO-B by 1-deprenyl after selective inhibition of MAO-A component by clorgyline. The results are expressed as percent enzyme activity towards phenylethylamine and (^{14}C)-deprenyl bound. Complete enzyme inactivation by 1-deprenyl results in 1 mole of inhibitor being bound per mole of enzyme per mole flavin[52].

sues[16, 18, 42, 50, 56, 62, 68]. Of interest to the present discussion is that while the ratio of the two enzyme forms is 1 : 1 in rat brain, this ratio is significantly in favor of MAO-B in human brain[4, 8, 18, 42, 43, 50, 68, 70]. Both forms of MAO in the liver and brain contain the same covalently bound cysteinyl-FAD co-factor at their active centers[52, 53, 59] (fig. 1) but differ in their substrate and inhibitor recognition sites[27]. It is thought that MAO-A and B may be separate gene products or else the result of post-translational modification of a single gene product[7, 12, 13, 29, 60]. By all accounts the human platelet contains only the B form whose properties are similar to enzyme B in other tissues[14, 19, 62, 63, 65] (table 2). The selective inhibitors (^{14}C)-clorgyline, (^{14}C)-deprenyl and (^{14}C)-pargyline bind stoichiometrically and irreversibly (mole/mole) to the N-5 of the cysteinyl-flavin co-factor[52] (figs 1 and 2). This property has rendered the use of selective inhibitors as a means to titrate the molecular turnover number of MAO in normal, pathological and physiological conditions where an alteration in enzyme activities have been noted[16, 70, 71].

Platelet and serotonergic neurone MAO activity

The analysis of MAO activity in human tissues have revealed that while the platelet contains only MAO-B[14, 19, 65, 70], both enzyme forms, with different ratios, are present in the various regions of the brain. This ratio is in favor of MAO-B, specially in the extra-pyramidal regions[8, 42, 65]. On occasions it has been speculated that the platelet-MAO activity is a reflection of central 5-HT neurone[43]. Although substantial MAO-B activity has been identified in the 5-HT neurones of raphe nucleus[22, 23, 35, 60] selective MAO-B inhibitors such as 1-deprenyl hardly affects 5-HT concentration in rat and human brain[22, 23, 50, 61]. By contrast clorgyline causes a substantial increase of brain 5-HT[4, 22, 23, 61]. It is thus an oddity that while MAO-B inhibitor, 1-deprenyl, alone has no influence on brain 5-HT, in combination with clorgyline it causes a further increase in 5-HT which is substantially higher than that observed with clorgyline alone[22, 23, 62]. The mechanism of this phenomenon is not well understood but has been attributed to the affinities of MAO-A and B for the neurotransmitter[17]. Thus, when MAO-A is selectively inhibited, the 5-HT concentration within the neurone may rise to a point that would satisfy the Km of MAO-B for 5-HT and be oxidized by it[22]. Such findings are a contradiction to platelet being a true representative model of 5-HT neurone, since Pletscher has shown that total inhibition of MAO in the platelet has no net effect on 5-HT uptake by the platelet. An analog situation also exists in the adrenal chromaffin cells, where in contrast to the presence of MAO-A in the adrenergic neurones, these cells also contain only MAO-B and MAO inhibition does not alter their catecholamine concentrations[46, 57]. The indications are that unlike the neuronal MAO-A, the B form in the above two 'models' of aminergic neurones do not have a direct functional regulatory role for noradrenaline and 5-HT metabolism. The need, therefore, arises to question what is the importance of MAO-B within the 5-HT neurone and the platelet and whether in the CNS there is some other endogenous MAO-B substrate which can modulate either the presynaptic release or the postsynaptic function of 5-HT.

Physiologically the function of MAO may be related to its location in the particular organ or cell. While it is accepted that intraneuronal MAO-A operates to maintain the cytoplasmic concentration of amines (dopamine, noradrenaline and 5-HT) within the neurone low, in the small intestine this enzyme is responsible for the inactivation of indirectly acting sympathomimetic amines (e.g. tyramine and phenylethylamine) or other amines, derived from their precursor amino acids as a result of bacterial enzymic decarboxylation[63, 64, 68]. Liver MAO may be responsible for controlling the blood concentrations of the amines. The highly active MAO of blood vessels and the lung could have a crucial role in protecting systemic organs from the toxic effect of circulating vasoactive monoamines[67].

We have already demonstrated the ability of the lung to actively take up 5-HT and phenylethylamine and deaminate them[67]. The oxidation of 5-HT is thought to be brought about by the capillary endothelial cells, with which the platelet intimately interacts[2, 3, 67]. The presence of only MAO-A in these cells[2] and its highly sensitive regulation by steroid hormones[2] suggests that capillary endothelial cells may be the metabolic barrier for the 5-HT and noradrenaline

released from the platelet during their interaction[3]. Even so, the function of MAO-B within the platelet remains unclear. The platelet, therefore, may be responsible ultimately for the non-chemical inactivation of circulating 5-HT[10] by the process of uptake and storage. This can readily be explained by the greater affinity ($\cong$ 1 μM) of vesicular uptake system[43] than the apparent Km of MAO-B (1200 μM) for 5-HT[17]. The primary presence of MAO-B in the platelet is consistent with our understanding of the physiology of these cells and the need to preserve 5-HT. An analogous situation exists in the adrenal chromaffin cell, which can store the highest concentrations of catecholamines without the latter being deaminated[46, 57]. In this case the MAO in the chromaffin cell is also entirely type B[71]. However, there is a significant difference between the MAO-B present in platelet and that in the chromaffin cell. The apparent Km of MAO-B in the chromaffin cell for noradrenaline and 5-HT are 1100 and 380 μM respectively[66]. This is in sharp contrast to the values for the platelet enzyme where the Km values are reversed[20]. Thus, although both platelets and chromaffin cells contain MAO-B, their kinetic and substrate specificities indicate the presence of two variants of the type B, even though their kinetics for the MAO-B substrates are almost identical. The presence of MAO-B in the platelet certainly enhances the capability of significant 5-HT storage for emergency peripheral use and prevention from non-physiological release. The latter hypothesis is further supported by the observation that arylalkylamines, tyramine, phenylethylamine, *p*-methoxyphenylethylamine and *p*-chloroamphetamine cause a concentration-dependent release of 5-HT from normal and reserpine-treated platelets and in vivo from rat brain[1, 30, 44, 45]. Indeed with the exception of *p*-chloroamphetamine, the above arylalkylamines are substrates of MAO-B, and MAO inhibitors enhance their releasing effects[1, 6, 30, 45]. Thus an MAO-B in the platelet and 5-HT neurones may also be a prerequisite for prevention of release by these indirectly acting sympathomimetic amines, which themselves may be present in the circulation and readily cross the blood brain barrier or the platelet membrane.

The use of platelet MAO-B

Much has been written about the numerous investigations on the use of platelet MAO as a biological marker of central monoaminergic neurones for depression, schizophrenia and alcoholism. However, these studies consistently have come under great criticism and a recent review on the subject point out 'although the study of central monoaminergic processes in some psychiatric diseases may be essential to our further understanding and treatment of these illnesses, the usefulness of platelet MAO activity as a monitor may be limited. Not only is the link between platelet MAO-B activity and central monoaminergic turnover not yet proven but there are also a great many uncontrollable nonpsychiatric variables that can affect both platelet MAO activity and platelet function'[19].

However, where platelet MAO activity monitor could be useful would be in cases where non-selective MAO (phenelzine) and selective MAO-B (1-deprenyl) inhibitors are employed as antidepressant and anti-Parkinson drugs respectively[11, 15, 33, 38–40, 42, 46]. Such an approach may be valid since these drugs have been shown to be clinically effective[5, 39, 41, 47]. The basis of their clinical use has found support in studies on the kinetic and inhibitor characteristics of MAO-B in the platelet, human brain and beef liver, which show close similarities. The most actively oxidized substrates are A–B (tyramine and dopamine) and B substrates (tables 1 and 2). The clinical therapeutic doses of phenelzine and 1-deprenyl which are sufficient to fully inhibit platelet MAO-B would on all accounts inactivate brain MAO-B[5, 14, 33, 39–41, 47]. Although no data on brain MAO activity after phenelzine treatment is available, therapeutic doses of a similar hydrazine derivative (isocarboxazide) fully inactivates the human MAO-A and B activities measured in autopsy samples[70]. The consequence of this inhibition is a substantial increase of brain 5-HT, noradrenaline and dopamine[4]. By contrast 1-deprenyl selectively inhibits platelet[5] and brain MAO-B[50] in Parkinsonian patients and induces increased brain dopamine and phenylethylamine[48–50]. Although in these brains MAO-A is also inhibited (< 70%), this in itself is not adequate to allow increased accumulation of 5-HT or the decrease of 5-hydroxyindoleacetic acid. Thus animal and human brain MAO inhibition studies have revealed a need for MAO inhibition of more than 80% before the clinical responses and changes in brain monoamines are to be noted[19, 22, 23, 48–50]. It is more than a casual interest that clorgyline (selective MAO-A inhibitor) which has a significant antidepressant activity (CF 68) is unable to inhibit either the platelet or human brain MAO-B[62] but causes a significant increase of brain 5-HT[4, 22, 23, 61]. Therefore, the situation remains where there is no adequate procedure for direct monitoring of human MAO-A activity, the enzyme form responsible for intraneuronal inactivation of neurotransmitters, noradrenaline and 5-HT, implicated in the pathophysiology of depressive illness[63, 64].

A novel approach to anticonvulsant therapy: The roles of brain and platelet MAO-B

It is well recognized that amino acids are the most universally distributed neurotransmitters in the central nervous system of mammals. GABA (γ-aminobutyric acid) and glycine are the principal brain inhibitory transmitter substances[9, 36, 51]. Thus pharmacological enhancement of the inhibitory action of these neurotransmitters is a rational approach to therapy of myoclonus, epilepsy, Huntington Chorea, tardive dyskinesia, and other neurological disorders where they have been implicated. However, neither of the two amino acids can cross the blood brain barrier readily. Although the antimyoclonic and antiepileptic actions of GABAergic drugs are well known[9, 38], there are no established mechanisms for enhancing glycinergic inhibition, either by increasing its brain concentration or using glycine agonists.

There now seems a procedure at hand to increase either brain GABA or glycine, in the absence of drugs that would inhibit their metabolism via transamination or decarboxylation. Milacemide (2-*n*-pentylaminoacetamide) (fig. 3 and tables 1 and 2) is a unique anticonvulsant that readily crosses the blood brain barrier (BBB) and is actively converted in the

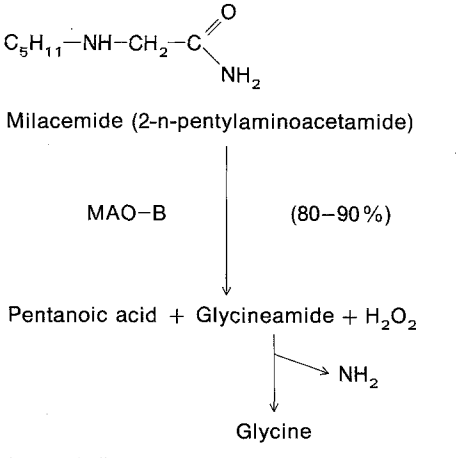

Figure 3. The metabolic pathway of milacemide in the rat brain.

brain to its major (90%) metabolites, glycineamide and glycine[51].

Structurally, milacemide is a glycine derivative of pentylamine, which is a selective substrate of MAO-B[54]. The oral administration of milacemide results in a significant increase in the concentration of glycine in the forebrain, cerebellum and medulla, but not in other tissues such as liver and kidney[51]. The secondary amine nature of milacemide suggested the *N*-dealkylation to glycineamide could involve the oxidative process of MAO. Our in vitro, in vivo and ex vivo studies have clearly shown milacemide to be a selective substrate of MAO type B[58, 72]. These results are substantiated by the kinetic parameters of milacemide oxidation using enzyme preparations which contained only MAO-B (human platelet and brain and beef adrenal chromaffin cell) or MAO-A (human placenta) (table 2). Furthermore, the oxidation of milacemide is selectively inhibited by inhibitors of MAO-B (1-deprenyl and AGN 1135) rather than by clorgyline, the MAO-A inhibitor.

The ability of MAO-B to oxidize the secondary amine milacemide are exciting for a number of reasons. Milacemide oxidation to glycine, an inhibitory neurotransmitter, without any severe clinical side effects[51] distinguish it from other drugs which primarily act on inhibitory neurones. The presence of only MAO-B in the platelet would allow the monitoring of its metabolism in the brain and clinical response to it. Finally, the unusual oxidative property of MAO-B opens the prospects for the development of similar compounds derived from GABA, glutamate, aspartate, taurine and β-alanine, which by themselves do not cross the blood brain barrier. Thus, a procedure for amino acid neurotransmitter replacement therapy of neurological disorders where these substances have been implicated is at hand. It remains to be seen whether the platelet system could be used as a model for the study of pharmacological activity of such drugs as milacemide. At least the first requirement, namely MAO-B, is present in this organelle.

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