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Inhibition of Monoamine Oxidase from Bovine Retina by β-Carbolines

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Abstract—The behaviour of some β-carboline derivatives as inhibitors of monoamine oxidase has been studied in bovine retina. Inhibition was found not to show any significant time dependence. Di- and tetrahydro-β-carbolines were shown to behave as reversible and competitive inhibitors. In contrast, the fully unsaturated β-carbolines harmane, harmine and harmaline, which showed deviation from linearity at high substrate concentrations, behaved as tight-binding inhibitors. In these cases, the concentration of the enzyme and the inhibitor were of the same order. This was confirmed by the K_i values for these compounds in the nanomolar concentration range. Consistent with this was that inhibition was only partly reversed by dialysis for 18 h at 4°C, although complete reversal was observed after dialysis for the same period at 37°C. Structure-activity relationships indicated that substitution of a methoxy group at the C7 position of the aromatic ring is determinant for this tight-binding behaviour; a substitution of this group at the C6 position greatly reduced inhibition. Since β-carbolines have been reported to be formed endogenously, this suggests that they might have important physiological actions on monoamine oxidase activity in-vivo. In contrast, all the β-carbolines investigated in this study had low potencies as inhibitors of monoamine oxidase B.

The 1,2,3,4-tetrahydro-β-carbolines (THβCs), are tricyclic compounds structurally related to the indoleamines. They have been extracted from plants used for their hallucinogenic properties (Schultes & Hofman 1973; Airaksinen & Kari 1981). They have also been found in foodstuffs, dairy products and alcoholic beverages (Beck & Holmstedt 1981).

The THβCs are endogenously formed from cellular condensation (Pictet-Spengler) of indoleamines or tryptophan with aldehydes or α-ketoacids (Kermack & McKail 1961), or by enzymatic formation from tryptamine and 5-methyltetrahydrofolic acid (Hsu & Mandell 1975).

Interest in these compounds derives from their pharmacological effects and it has been proposed that they act as endogenous neuromodulators by altering monoamine release, re-uptake and metabolism (Buckholtz 1980). Metabolism is affected by monoamine oxidase (MAO) inhibition, although previous studies reported that the THβCs were relatively poor MAO inhibitors (Buckholtz & Boggan 1977). This may have been because of failure to differentiate between MAO-A and MAO-B by using tryptamine, which is a common substrate of both MAO forms, to determine enzyme activity. Furthermore, all the studies reported on the effect of THβCs on MAO activity have been limited to determination of IC50 values and there has been a lack of more complete kinetic studies on the interaction of these compounds with each of the MAO forms.

In bovine retina, the biogenic amines play a role as neuromodulators of the visual function, and dopamine may be involved in the control of signal transmission (Wulle et al 1990). Furthermore, dopamine metabolism by the different amine oxidases present in bovine retina (Fernández de Arriba et al 1991) could be altered by THβCs and their endogenously-formed derivatives.

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Recently, 3-4-dihydro-β-carbolines and β-carbolines have been proposed to be endogenous candidates that may induce parkinsonism (Drucker et al 1990) and it has been reported that they can inhibit dopamine uptake (Rommelspacher et al 1978; Komulainen et al 1980) and the mitochondrial respiratory chain (Albores et al 1990).

In view of the potential importance of the β-carboline derivatives, we have studied the kinetics of interactions with MAO from bovine retina. These studies were designed to establish the inhibitory potency of these compounds on MAO activity in-vitro so that their possible roles of regulation of dopamine metabolism in bovine retina could be assessed.

Materials and Methods

The β-carboline analogues, harmane, harmine, harmol and 6-methoxy-harmane; the 3,4-dihydro-β-carbolines, harmaline, harmalol, 6-methoxy-harmalan; and the 1,2,3,4-tetrahydro-β-carbolines, tetrahydronorharmane and 6-methoxy-tetrahydronorharmane, were purchased from Sigma, UK.

Bovine retina was prepared as described previously (Fernández de Arriba et al 1991), and stored at −18°C as 0·5-mL samples at a protein concentration of 1 mg mL^{-1} in 50 mM potassium phosphate buffer, pH 7·2.

MAO activity was measured radiochemically at 37°C by the method of Fowler & Tipton (1981), with β-phenylethylamine (22·2 μM) or 5-hydroxytryptamine (5-HT) (100 μM) used as substrates. The reaction took place in a final volume of 225 μL 50 mM potassium phosphate buffer pH 7·2, containing 200–400 μg protein and was stopped by the addition of 100 μL 2 M citric acid. The products were extracted with toluene/ethyl acetate 1:1 (v/v) containing 0·6% (w/v) 2,5-diphenyloxazole and the radioactivity was measured in a scintillation counter.

Inhibition curves with different derivatives of the

β-carbolines, were determined by incubating retina samples at different inhibitor concentrations (range 10^{-3}–10^{-11} M) for 10 min at 37°C. After this period, the remaining activities were determined towards radiolabelled (100 μM) 5-HT (a specific MAO A substrate) and (22 μM) β-phenylethylamine (a specific MAO B substrate). These substrate concentrations were close to their respective K_m values (Fernández de Arriba et al 1991) so that possible competitive inhibitory effects could be observed. At each substrate concentration used, reaction time curves were constructed to ensure that initial rates were measured.

Protein concentration was determined by the method of Hartree (1972), with bovine serum albumin as standard.

The time-dependence of the inhibitory processes was determined at inhibitor concentration that gave approximately 60% inhibition after an incubation period of 30 min. After different times of preincubation of each inhibitor (500 μL) with 500 μg enzyme in a total volume of 2·5 mL 50 mM potassium phosphate buffer pH 7·2, 100 μL of this mixture was assayed for MAO-A activity by a radiochemical method.

The reversibility of the inhibition process was assayed by dialysis (Visking dialysis tubing, exclusion limit 8000–15 000 Da Serva Feinbiochemica GmbH & Co.). One millilitre of enzyme was incubated with 0·5 mL of each inhibitor (to give about 70% inhibition) in a total volume of 2·5 mL buffer. After 10 min incubation at 37°C, the reaction was stopped by chilling it in an ice-bath, and the remaining activity was measured towards radiolabelled 5-HT as substrate. The samples were then dialysed against 1000 vol buffer at 4°C for 18 h (three buffer changes) and the remaining activity was again measured. Dialysis was also performed at 37°C for 18 h in those cases where activity was not regained after dialysis at 4°C. Controls were taken through the same procedure in the absence of inhibitor.

Kinetic constraints were determined spectrophotometrically using kynuramine as substrate. To ensure that only MAO-A activity was measured, the tissue samples were preincubated with 1 μM l-deprenyl at 37°C for 60 min before assay. The appearance of product was monitored at 324 nm in a Perkin-Elmer Lambda 2 spectrophotometer equipped with an automatic six-cell changer, in the absence and presence of different inhibitor concentrations (10^{-5}–10^{-9} M). The final incubation volume was 2 mL 50 mM potassium phosphate buffer, pH 7·2, containing 500 μg retina protein and kynuramine in the concentration range 25–250 μM. The extinction coefficient was taken to be 20 000 M^{-1} as previously determined by Avila et al (1993). Inhibition kinetic parameters were determined by nonlinear regression analysis using the computer program Enzfitter (R. J. Leatherbarrow, Elsevier-Biosoft, London), except for those compounds that gave tight-binding inhibition behaviour. The graphical method of Dixon (1972) was used to analyse tight-binding inhibition. Double-reciprocal plots of data are presented for illustrative purposes only.

Results

Fig. 1 shows the chemical structure of some of the carboline analogues studied. Fig. 2 shows the percentage of MAO-A and MAO-B activities from bovine retina remaining after

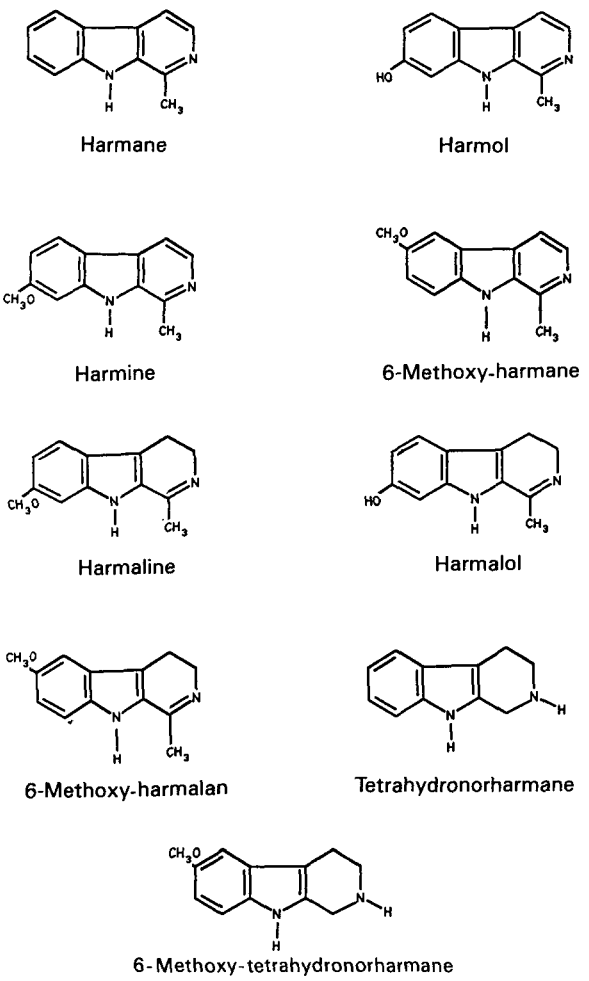

FIG. 1. Structures of the β-carbolines (harmane, harmol, harmine and 6-methoxy-harmane), the 3,4-dihydro-β-carbolines (harmaline, harmalol and 6-methoxy-harmalan) and the 1,2,3,4-tetrahydro-β-carbolines (tetrahydronorharmane and 6-methoxy-tetrahydronorharmane) used in this work.

incubation with different harmine concentrations as a representative inhibition curve. All β-carboline derivatives tested were potent MAO-A inhibitors while having little effect on the deamination of β-phenylethylamine. In all the cases the IC50 values for MAO-B activity were greater than 1 mM.

The IC50 values of these compounds assayed as inhibitors of the 5-HT deamination in bovine retina are shown in Table 1. These values are compared with those reported for the inhibition of the enzyme from mouse brain and liver by Buckholtz & Boggan (1977).

In terms of decreasing potency as MAO-A inhibitors, the group of compounds are ordered as follows: β-carbolines, 3,4-dihydro-β-carbolines and 1,2,3,4-tetrahydro-β-carbolines.

Inhibition by all the compounds was found not to be affected by incubation of the enzyme and inhibitor for 30 min at 37°C before the addition of substrate (data not shown).

In order to determine the reversibility of the inhibition process, MAO-A was incubated with sufficient inhibitor to give approximately 70% inhibition in each case and the

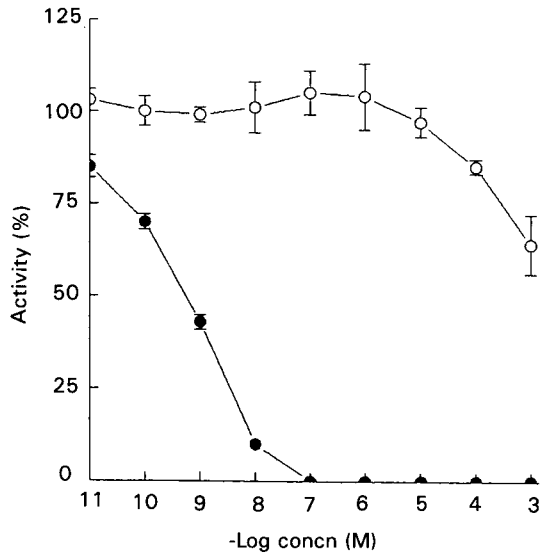

FIG. 2. Inhibition of the monoamine oxidase activity towards 5-HT (100 μM, ●) and β-phenylethylamine (20 μM, ○) by harmine. Tissue samples were pre-incubated for 10 min at 37°C with different inhibitor concentrations (10^{-11}–10^{-3} M). The remaining activity is expressed as percentage of the control activity, determined in the absence of inhibitor. Each value is the mean ± s.e.m. of three experiments.

samples were then dialysed. Activity was recovered after dialysis overnight at 4°C in all cases with the exception of all harmane, harmine, and harmaline (Table 2).

The high potencies of some of the β-carbolines (harmane, harmine and harmaline) indicated that the concentration of the inhibitor and the enzyme in these studies were of the same order. Since the inhibition was not time-dependent, but was not fully reversed after overnight dialysis, they could be behaving as tight-binding inhibitors. To check this possibility, enzyme-inhibitor mixtures were dialysed at 37°C for 18 h. This resulted in essential complete recovery of activity, confirming that a reversible tight-binding inhibitory process was involved (Table 2).

The kinetic parameters for inhibition were determined as described in Materials and Methods. Double-reciprocal plots of the inhibition by harmine are shown as an example in Fig. 3. A clear deviation from linearity was observed at high substrate and high inhibitor concentrations, showing a typical downward curvature of tight-binding inhibitory behaviour. Such deviation was observed only with those derivatives that presented the lowest IC50 values and with which the inhibition only reversed after dialysis at 37°C (harmane, harmaline and harmine; Table 2). The remainder of the compounds behaved as reversible and competitive MAO A inhibitors and the kinetic data, calculated by non-linear regression analysis, are shown in Table 3.

The K_i values for the tight-binding inhibitors harmane, harmine and harmaline, were determined according to the method of Dixon (1972). A Dixon plot of initial velocity vs harmine concentration, with 50 μM kynuramine as substrate, is shown in Fig. 4 as a representative example. The graph will fall from a starting value, V_0, to the baseline. This initial velocity is far from the V_{max} value since the inhibition curve may have been determined with a substrate concentration that was less than saturating. This curve was obtained by each kynuramine concentration in the range of 25–250 μM.

Table 1. Inhibition of MAO A from bovine retina by β-carbolines.

Compound	IC50 (nM) MAO-A	*IC50 (nM) MAO-A
Harmane	30 ± 10	3300
Harmol	80 ± 20	5800
Harmine	1 ± 0·3	80
6-Methoxy-harmane	500 ± 20	3100
Harmaline	7 ± 3	60
Harmalol	100 ± 20	10000
6-Methoxy-harmalan	2000 ± 300	18000
Tetrahydronorharmane	8000 ± 400	58000
6-Methoxy-tetrahydro-norharmane	8000 ± 300	58000

IC50 values were determined as described in the text. Values are expressed as means ± s.e.m. (n = 3). * Data taken for comparative purposes from the results of Buckholtz & Boggan (1977) for the inhibition of MAO from mouse brain and liver.

Table 2. Percent activity recovered from MAO-A incubated with different β-carbolines, after dialysis for 18 h at 4 and 37°C, respectively. Initial inhibitor concentrations were chosen to give approximately 70% inhibition. Other details are given in the text.

Compound	% Activity recovered after 4°C dialysis	% Activity recovered after 37°C dialysis
Harmane	66 ± 5*	87 ± 3
Harmol	80 ± 2	87 ± 4
Harmine	44 ± 1*	88 ± 9
6-Methoxy-harmane	86 ± 7	102 ± 2
Harmaline	56 ± 2*	89 ± 2
Harmalol	93 ± 6	99 ± 3
6-Methoxy-harmalan	85 ± 8	92 ± 2
Tetrahydronorharmane	90 ± 4	99 ± 3
6-Methoxy-tetrahydronorharmane	84 ± 4	97 ± 2

*$P < 0.05$ compared with activity recovered after 37°C dialysis.

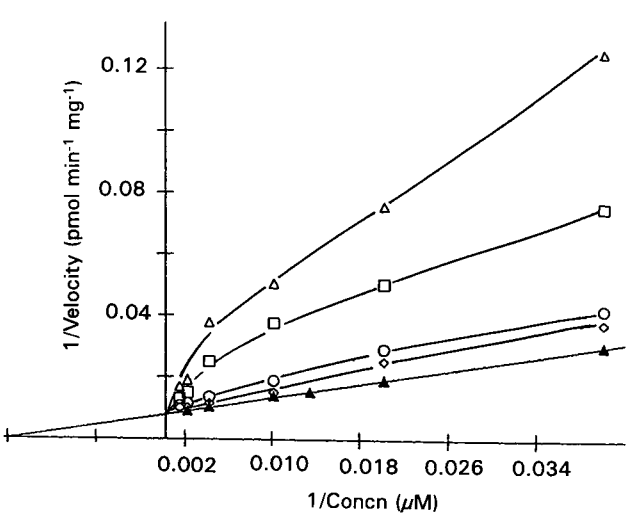

FIG. 3. Double-reciprocal plots for the deamination of kynuramine by MAO-A in the presence of different harmine concentrations. △ 5×10^{-8}, □ 10^{-8}, ○ 10^{-9}, ◇ 10^{-10} M and ▲ in the absence of the inhibitor. The assay conditions are described in the text. Each point is the mean of three determinations.

Table 3. Kinetic inhibition parameters of β-carbolines and structurally related compounds on MAO-A from bovine retina.

Compound	K_i (nM)	Type of inhibition
Harmane	27 ± 1	Tight binding
Harmol	155 ± 8	Competitive
Harmine	3·8 ± 0·5	Tight binding
6-Methoxy-harmane	872 ± 20	Competitive
Harmaline	6·7 ± 0·3	Tight binding
Harmalol	273 ± 5	Competitive
6-Methoxy-harmalan	597 ± 8	Competitive
Tetrahydronorharmane	1850 ± 203	Competitive
6-Methoxy-tetrahydro-norharmane	1750 ± 140	Competitive

Values from initial rate data were obtained at 37°C by the procedures described in the text. The concentration range used for kynuramine was 25–250 μM. The concentration range of inhibitor used varied around the IC50 value in each case. Values are expressed as means ± s.e. of duplicate measurements in each of two separate experiments.

If lines are drawn through the points of the curve at which V = Vo/2, Vo/3, Vo/4 etc., they will intercept the abscisson at equidistant points. Different values of the distance K were obtained at the different kynuramine concentrations assayed (Dixon 1972). When these K values were plotted as a function of the kynuramine concentration, a straight line was obtained whose intercept with the y-axis represents the K_i of inhibition and intercepts with the x-axis at the K_m value.

The inhibition constants determined for all the compounds studied are shown in Table 3. As would be expected the tight-binding inhibitors, harmane, harmine and harmaline, were the most potent inhibitors with a K_i value in the nanomolar range. In the β-carbolines, the substitution of an H at the C7 position (harmane), by a methoxy group (harmine), increases the inhibitory potency approximately tenfold. This compound was the most potent inhibitor of MAO A in bovine retina with a potency similar to that of clorgyline (Fernández de Arriba et al 1991). The opposite effect was observed when a hydroxy group was substituted at the same position (harmol), with the inhibitory potency decreasing to about one-fifth. When a methoxy group was located at the C6 position (6-methoxy-harmane), the inhibitory potency diminished by about 800 times. These kinetic data differ from some of those reported by Nelson et al (1979) on the inhibition of rat brain MAO. In this case, the K_i value reported for harmane was about four times greater than the value calculated by us. However, Nelson et al were not able to detect the tight-binding inhibitory behaviour under the conditions used in their work.

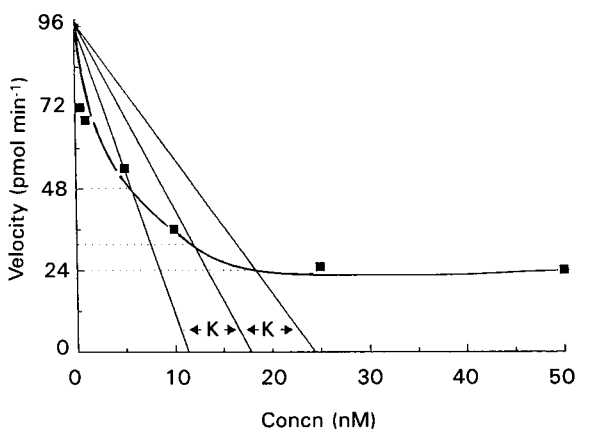

FIG. 4. A Dixon (1972) plot of initial velocity against harmine concentrations using kynuramine (50 μM) as substrate.

In the case of 3,4-dihydro-β-carbolines, harmaline, with a methoxy group at the C7 position, was found to be the most potent tight-binding inhibitor, but when an H at the C7 position was substituted by an OH group (harmalol), the affinity decreased to one quarter. A decrease by a factor of nine in affinity resulted when a methoxy group was located at the C6 position (6-methoxy-harmalan).

The 1,2,3,4-tetrahydro-β-carbolines were the least potent MAO A inhibitors of the compounds studied, with K_i values in the μM range. These results are in agreement with those reported by Meller et al (1977), on rat brain MAO, despite the fact that they did not inhibit the MAO-B activity in their preparation and used a substrate concentration that would have detected the activities of both monoamine oxidases.

Discussion

The results presented here show β-carbolines to be the most potent MAO-A inhibitors followed by the 3,4-dihydro-β-carbolines and the 1,2,3,4-tetrahydro-β-carbolines. None of these compounds significantly inhibited MAO-B. They also allow us to establish some structure-activity relationships for the β-carbolines: the presence of a methoxy group at the C7 position of the heterocyclic ring enhances the inhibitory potency towards MAO A in bovine retina, but its replacement by an OH group at the same position or a methoxy group at the C6 position, showed an opposite effect. These conclusions also apply to the 3,4-dihydro-β-carbolines whereas substitution of a methoxy group at position C6 of tetrahydronorharmane had no significant effect on inhibitory potency.

This is the first study to report the kinetic behaviour of β-carboline derivatives as MAO A inhibitors in the retina. The potency of their actions as MAO inhibitors, particularly the tight-binding compounds harmane, harmine and harmaline, indicates that they could have important physiological actions in this tissue, even if formed in only very small amounts in-vivo.

Buckholtz & Boggan (1977) studied the inhibition of MAO activity from mouse brain by these compounds. Only IC50 values were reported and these were about ten times those reported in the present work (see Table 1). Although this discrepancy might involve a species or tissue difference, a major factor is probably the failure of Buckholtz & Boggan to discriminate between the effects on MAO-A and MAO-B through the use of tryptamine, which is a substrate for both forms of MAO. The IC50 values reported here are broadly similar to those reported for the inhibition of the MAO-A form from rat liver by β-carbolines (Glover et al 1982) and for the effects of tetrahydro-β-carbolines on the activity of rat brain MAO-A (Meller et al 1977), although neither of those studies determined the type of inhibition involved.

The β-carbolines have been reported to interact specifically with a number of aspects of 5-HT-ergic neurotrans-

mitter function, altering its metabolism, reuptake and release. It is possible that β-carbolines also affect other neurotransmitter systems (Buckholtz 1980) and tetrahydro-β-carbolines have been reported to inhibit dopamine uptake by the brain synaptosomes in-vitro (Rommelspacher et al 1978; Komulainen et al 1980).

Dopamine is a neurotransmitter present in the amacrine cells or interplexiform cells of bovine retina which may also play an important role as a neuromodulator (Wulle et al 1990). Dopamine induces a decrease in the permeability of gap junctions between the horizontal cells in some species (Teranishi et al 1983) by a process acting through D_1 receptors, linked to the stimulation of adenylate cyclase. Dopamine, acting on D_2 receptors linked to the inhibition of adenylate cyclase, modulates the contractile machinery of photoreceptors (Deary & Burnside 1988). Catecholamines are metabolized in most tissues by catechol-*O*-methyl transferase and monoamine oxidase. We have shown transferase activity to be absent from bovine retina (unpublished data). In that tissue it appears that dopamine is metabolized exclusively by the amine oxidases. This depends on the amine concentration, but MAO-A is essentially completely responsible for dopamine deamination when the concentrations of neurotransmitter are low (μM) (Fernández de Arriba et al 1991).

The high potency and specificity of the different β-carboline derivatives as MAO-A inhibitors in bovine retina suggest that they may be involved in the modulation of this enzyme in-vivo. Further work on the concentration of these compounds within retinal tissues in-vivo and their variations in response to physiological stimuli will be necessary before a possible role in controlling the 5-HT and dopamine levels in this tissue, and consequent effects of visual function, might be established.

Acknowledgements

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