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CONTRIBUTION OF DIFFERENT AMINE OXIDASES TO THE METABOLISM OF DOPAMINE IN BOVINE RETINA

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Abstract—The contribution of monoamine oxidase (MAO) A, MAO B and semicarbazide-sensitive amine oxidase (SSAO) to the metabolism of dopamine in the bovine retina was studied. These activities were present in the optic nerve, iris, choroid and bovine retina, but they were absent in the lens. SSAO activity towards dopamine was present in the choroid and the retina, but not in the iris or the optic nerve. The corresponding kinetic values for this substrate in the retina and the choroid showed higher affinity for MAO A (K_m 271 and 197 μM, respectively) than for MAO B (K_m 861 and 404 μM, respectively). This effect was counteracted by the higher V_{max} value for MAO B resulting in the V_{max}/K_m ratio being similar for both cases. The absence of detectable SSAO activity towards dopamine in these last two tissues contrasts with the presence of that enzyme when benzylamine was studied as substrate. These results indicate that two different SSAO activities could be present in the bovine eye.

The biogenic amines are metabolized by one or both of the two forms of monoamine oxidase (MAO†) [monoamine:oxygen oxidoreductase (deaminating) (flavin-containing), EC 1.4.3.4]. MAO A and B can be distinguished by their different sensitivities towards the acetylenic inhibitors, clorgyline and 1-deprenyl, and their substrate specificities. 5-HT is a prefered substrate for MAO A and PEA is a prefered substrate for MAO B.

The presence of another amine oxidase different from MAO has been detected in many studied tissues. The activities of this enzyme are particularly high in the blood vessels, especially the aorta, and in highly vascularized tissues. This amine oxidase is resistant to inhibition by clorgyline and sensitive to inhibition by carbonyl reagents such as semicarbazide. Consequently it has been named semicarbazide-sensitive amine oxidase (SSAO) [amine:oxygen oxidoreductase (deaminating) (copper containing), EC 1.4.3.6]. Benzylamine is a particularly good substrate for this enzyme but its physiological role is unclear [1]. This activity has been studied extensively in brown adipose tissues [2] and highly vascularized tissues, such as the aorta and the umbilical vein [3], but there have been no reports on its behaviour in the retina, a tissue which must be regarded as a part of the central nervous system on the basis of its embryonic derivation, morphological organization and function.

It has been suggested [4] that biogenic amines play an important role as neuromodulators of the visual function. Although dopamine, noradrenaline, serotonin and adrenaline are all strong candidates for the role of transmitter in the central nervous system, only dopamine has reached this status in the retina as well as in the visual system [5, 6]. It has also been reported that dopamine, located in amacrine and/or interplexiform cells, could act as a neuromodulator involved mainly in the control of signal transmission [7]. Changes in dopamine levels may also provide an adaptational signal for the retinal neural network [7, 8]. Favard *et al.* [9] have recently presented ultrastructural evidence for an intimate relationship between dopamine cell processes and retinal capillary walls in monkey and rat. However, these workers noted that the absence of any data on amine oxidase activities in retinal structures precluded attempts to understand the possible role of degradative processes in controlling the levels of this neurotransmitter.

These observations have prompted us to investigate the metabolism of dopamine in the retina. Dopamine is metabolized by both forms of MAO in rat and human brain [10]. However, it has also been reported that SSAO may contribute to the deamination of this amine in rat vas deferens [11].

The aims of this work were to determine the contributions of MAO A, MAO B and SSAO activities to the deamination of dopamine and other biogenic amines in the retina and other tissues of the bovine eye.

MATERIALS AND METHODS

Bovine eyes were obtained immediately after slaughter of the animals, packed in ice and transported to the laboratory from a local abattoir.

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† Abbreviations: MAO, monoamine oxidase; SSAO, semicarbazide-sensitive amine oxidase; 5-HT, 5-hydroxytryptamine, 5-hydroxy-[sidechain-α-^{14}C]tryptamine creatine sulphate; PEA, β-phenylethylamine, [ethyl-1-^{14}C]-phenyl-ethylamine hydrochloride; benzylamine, [7-^{14}C]benzylamine hydrochloride; dopamine, [7-^{14}C]dopamine hydrochloride; tyramine, [7-^{14}C]tyramine hydrochloride; tryptamine, [sidechain-2-^{14}C]tryptamine bissucinate.

The optic nerve was cut off and the cornea dissected by means of a circular incision at the corneoscleral junction. The iris, lens and vitreous body were removed, the eyeball was inverted, and the retina was detached by gently shaking in 50 mM potassium phosphate buffer, pH 7.2. Finally, the choroid was removed.

All samples were frozen in liquid N_2 and then disrupted mechanically, homogenized in 50 mM potassium phosphate buffer, pH 7.2 (1:10 w/v), filtered through gauze (110 μm) and stored in aliquots at −80°. In the case of the retina, the preparations were disaggregated by sonication at low frequency for 15 sec before each assay.

MAO activity was determined radiochemically at 37° by the method of Fowler *et al.* [12]. PEA (22.2 μM), benzylamine (1 and 100 μM), 5-HT (100 μM), tyramine (100 μM), dopamine (100 μM) and tryptamine (100 μM) were used as substrates. The reaction took place in a final volume of 225 μL of 50 mM potassium phosphate buffer, pH 7.2, containing 200–400 μg of protein and was stopped by the addition of 100 μL 2 M citric acid. The products were extracted into toluene/ethyl acetate 1:1 (v/v) containing 0.6% (w/v) 2,5-diphenyloxazole and the radioactivity was measured in a scintillation counter. SSAO activity was determined towards benzylamine (1 μM) as substrate under the same assay conditions.

Kinetic constants were determined from studies of the effects of substrate concentration on the initial velocity of MAO A or B, in preparations where the activity of the other form had been inhibited by preincubation for 60 min at 37° with 0.1 μM of l-deprenyl or clorgyline. These concentrations were found to inhibit the activity of one form of the enzyme completely without significantly affecting the activity of the other, in agreement with previous studies carried out in other tissues [13]. Higher concentrations of clorgyline (1 mM) were used to inhibit the activity of both forms of MAO so that the SSAO activity could be studied. For each substrate concentration used, reaction time courses were determined to ensure that initial rates were measured.

Inhibition curves with clorgyline, deprenyl, semicarbazide and KCN were carried out by incubating samples of enzyme at different inhibitor concentrations (range 10^{-3}–10^{-10} M) for 30 min at 37°. After this period, the remaining activities were determined towards the different substrates.

Protein concentration was determined by the Hartree method [14] with bovine serum albumin as standard.

RESULTS

Specific activities

The specific activities towards tyramine, 5-HT, PEA, dopamine and tryptamine were calculated in each part of the bovine eye. In each case linear relationships between the product formed versus time and versus enzyme concentration were obtained under the assay conditions used. The results are summarized in Table 1. No activity was detected in the cornea, lens or vitreous humor.

The optic nerve had the highest specific activity towards each of the substrates assayed, with the specific activity towards PEA being the lowest found in all the tissues. The activities towards dopamine were similar in all parts of the bovine eye that had detectable amine oxidase activity. The ratio MAO A/ MAO B was higher in the optic nerve (5.2) than in the iris and choroid (1.6), whereas the retina showed an intermediate value (2).

Sensitivity towards acetylenic compounds

The inhibitory effects of different clorgyline concentrations (10^{-3}–10^{-10} M) on MAO activities towards different amine substrates were determined in each part of the eye.

Figure 1 shows the inhibition curves of the MAO activity present in the retina towards dopamine, tyramine, PEA, tryptamine and 5-HT. A simple sigmoidal curve was obtained in the case of PEA and 5-HT. With the first of these substrates a higher clorgyline concentration was necessary to obtain total inhibition than was the case with 5-HT, indicating that under the conditions used PEA and 5-HT are metabolized in the retina by MAO B and MAO A, respectively. A double sigmoidal curve was obtained with each of the other substrates and the level of the plateau showed in all cases that the predominant activity towards tyramine and tryptamine was MAO A. In the case of dopamine about 10% of the activity was resistant to inhibition by 10^{-3} M of clorgyline. Thus, from these data, 10% of the activity towards dopamine was due to SSAO and 43% and 47% to MAO A and MAO B, respectively. Similar results were obtained with choroid (Fig. 2). In this case it was found that about 11% of the activity towards dopamine was resistant to inhibition by 1 mM of clorgyline. Broadly similar behaviour was observed with the preparations of optic nerve and iris but in these cases no residual activity was observed towards dopamine after inhibition by 1 mM of clorgyline (data not shown). Activation at low inhibitor concentrations was observed in some cases, an effect that has been described frequently.

Presence of SSAO activity

When the substrate assayed was benzylamine, an activity insensitive to inhibition by 1 mM clorgyline was found in all parts of the bovine eye, indicating the presence of SSAO. This was confirmed by determining the extent of inhibition caused by different concentrations of semicarbazide. Figure 3 shows the inhibition curves obtained with clorgyline and semicarbazide in the retina using 1 or 100 μM benzylamine as substrate. The behaviour was similar at both concentrations of this amine which indicates that MAO B and SSAO had similar K_m values towards benzylamine as substrate. Similar results (not shown) were obtained with the other eye tissues and in all cases the percentage of inhibition given by 1 mM semicarbazide corresponded to the proportion of the activity which was insensitive to inhibition by 1 mM clorgyline.

These results allows the contributions of the different amine oxidase activities to the oxidation of

Table 1. Amine oxidase activities in bovine eye tissues

Substrate	Iris	Optic nerve	Retina	Choroid
Tyramine	292.8 ± 23.2	751.5 ± 13.0	234.1 ± 13.2	175.5 ± 3.5
5-HT	164.4 ± 5.6	448.1 ± 40.2	176.2 ± 7.7	92.7 ± 3.7
PEA	98.0 ± 2.5	89.1 ± 6.5	88.1 ± 7.8	56.6 ± 5.3
Dopamine	426.7 ± 15.2	497.5 ± 40.3	393.3 ± 10.2	327.7 ± 20.5
Tryptamine	141.5 ± 5.6	476.3 ± 10.8	130.8 ± 8.3	100.7 ± 12.5

Values are pmol/min/mg protein and are expressed as means ± SEM (N = 4).

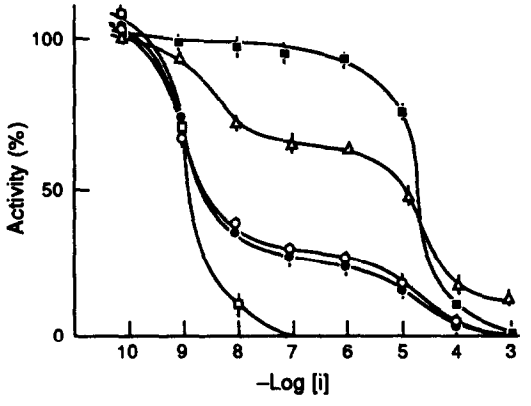

Fig. 1. Inhibition curves by clorgyline of the monoamine oxidase activities towards 5-HT (100 μM) (□), PEA (20 μM) (■), tyramine (100 μM) (○), tryptamine (100 μM) (●) and dopamine (100 μM) (△) as substrates in the retina. The samples were preincubated for 30 min at 37° with different inhibitor concentrations (10^{-10}–10^{-3} M). The remaining activity is expressed as percentage of control activity determined in the absence of inhibitor. Each value is the mean ± SEM (N = 3).

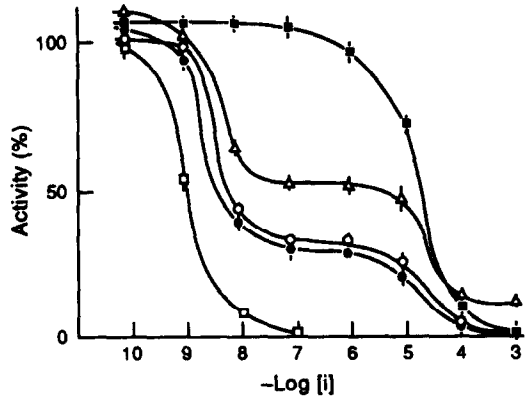

Fig. 2. Inhibition curves by clorgyline of the monoamine oxidase activities towards 5-HT (100 μM) (□), PEA (20 μM) (■), tyramine (100 μM) (○), tryptamine (100 μM) (●) and dopamine (100 μM (△) as substrates in the choroid. The samples were preincubated for 30 min at 37° with different inhibitor concentrations (10^{-10}–10^{-3} M). The remaining activity is expressed as percentage of control activity determined in the absence of inhibitor. Each value is the mean ± SEM (N = 3).

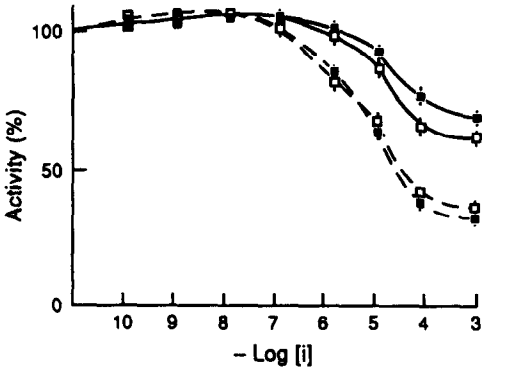

Fig. 3. Inhibition curves by clorgyline (---) and semicarbazide (——) of the amine oxidase activities towards benzylamine 1 μM (□) and 100 μM (■) as substrate in the retina. The samples were preincubated for 30 min at 37° with different inhibitor concentrations (10^{-10}–10^{-3} M). The remaining activity is expressed as percentage of control activity determined in the absence of inhibitor. Each value is the mean ± SEM, (N = 3).

the amine substrates assayed to be calculated. The results obtained are summarized in Table 2.

Kinetic parameters of MAO activities

MAO A and B were fully inhibited by incubation for 60 min at 37° with 3×10^{-7} M clorgyline or 3×10^{-7} M deprenyl, respectively. The activity of SSAO was inhibited by incubation under the same conditions with 10^{-3} M semicarbazide. The use of these inhibitory processes allowed the activity of each enzyme to be studied in the absence of any interference from the others.

K_m and V_{max} values were determined by non-linear regression analysis using the computer program Enzfitter (R. J Leatherbarrow, Elsevier-Biosoft, London). The results obtained are summarized in Table 3. The K_m values for 5-HT were similar in all the tissues, however, the V_{max} value was high in the optic nerve and low in the choroid. The pseudo first order velocity constant V_{max}/K_m was also highest in the optic nerve. In all cases, 5-HT was substrate only of the MAO A form. PEA was shown to be a selective substrate for MAO B with a lower K_m value towards this substrate. The high value of the V_{max}/K_m ratio also confirms PEA as exclusive substrate of MAO B.

Tyramine was a common substrate of both MAO forms, as was indicated by the inhibition curves. The

Table 2. Relative contributions of MAO B, MAO A and SSAO activities to the oxidation of different amines in bovine eye tissues

Substrate	Optic nerve			Retina			Choroid			Iris		
	MAO A	MAO B	SSAO	MAO A	MAO B	SSAO	MAO A	MAO B	SSAO	MAO A	MAO B	SSAO
Tyramine	85 ± 2	15 ± 2	—	71 ± 4	29 ± 4	—	70 ± 3	30 ± 3	—	73 ± 2	27 ± 2	—
Dopamine	83 ± 1	17 ± 1	—	43 ± 3	46 ± 3	10 ± 3	44 ± 3	45 ± 3	11 ± 3	73 ± 2	27 ± 2	—
Tryptamine	89 ± 2	11 ± 2	—	74 ± 4	26 ± 4	—	75 ± 3	25 ± 3	—	71 ± 4	29 ± 4	—
Benzylamine (100 μM)	—	68 ± 2	30 ± 2	—	69 ± 4	35 ± 4	—	56 ± 2	40 ± 2	—	60 ± 2	43 ± 2
Benzylamine (1 μM)	—	75 ± 3	25 ± 3	—	60 ± 5	36 ± 5	—	58 ± 4	41 ± 4	—	62 ± 3	40 ± 3
5-HT	100	—	—	100	—	—	100	—	—	100	—	—
PEA	—	100	—	—	100	—	—	100	—	—	100	—

Values are percentages and are expressed as means ± SEM (N = 3).

K_m values were similar for both forms of MAO in all the tissues studied but the V_{max} and V_{max}/K_m values indicate this substrate to be mainly deaminated by MAO A in all the tissues, with the optic nerve exhibiting the greatest activity. Similar results were obtained with tryptamine as the substrate.

In the case of dopamine, MAO A showed similar K_m values in all the tissues whereas the value towards MAO B was significantly higher. The corresponding V_{max}/K_m ratio was higher for a MAO A than for MAO B in the optic nerve and the iris, and in these tissues dopamine was metabolized mainly by MAO A. In the case of the retina and choroid these differences were less marked, and in these tissues dopamine was metabolized similarly by both MAO forms (see Table 2).

The kinetic parameters of MAO B and SSAO for benzylamine in the retina have also been determined. The concentration range used was 10 μM–1 mM and the kinetic constants measured were for MAO B, K_m = 167 μM and V_{max} = 128 pmol/min/mg protein, and for SSAO, K_m = 220 μM and V_{max} = 56 pmol/min/mg protein. The proportion of MAO B and SSAO contributing to the metabolism of benzylamine calculated from the corresponding specific activities at 1, 100 and 1000 μM is coincident with the data shown in Table 2. These results indicate that both enzymes in the retina have similar K_m values.

Contribution of MAO A, MAO B and SSAO to the deamination of dopamine

The kinetic parameters of MAO A, MAO B and SSAO towards dopamine estimated in the retina with different concentrations of this substrate (0.10–2 mM), after prior inhibition of the two other enzymes as described above, were used to calculate the contribution of each enzyme to the oxidation of this amine.

The curves calculated for the contribution of the three enzymes in the retina as a function of dopamine concentration are shown in Fig. 4. At a low dopamine concentration (100 μM) MAO A (43%) and MAO B (47%) contributed similarly to the metabolism of dopamine and SSAO only contributed about 10%. However, when the dopamine concentration increased, the relative importance of MAO A decreased whereas that of MAO B and SSAO increased. At 2 mM dopamine the relative contributions were 20% for MAO A, 44% for MAO B and 36% for SSAO. Thus, at high dopamine concentrations MAO B and SSAO were mainly responsible for the metabolism of this amine.

DISCUSSION

Studies with the amines tyramine, PEA, tryptamine, dopamine and serotonin indicated that both forms of MAO activity were present in the parts of the bovine eye. Of these amines only the latter two have been considered as neurotransmitters in the retina [8, 15]. The highest specific activities observed were present in the optic nerve although the activities towards dopamine were quite similar in all the tissues. The ratio of MAO A/B activity indicated that with tyramine as the substrate MAO A was the predominant metabolizing activity in all the tissues.

Table 3. Kinetic constants of MAO A and B for the metabolism of different amines in bovine eye tissues

Substrate	Optic nerve		Retina		Iris		Choroid	
	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B
Tyramine K_m	102.0 ± 7.9	110.2 ± 9.2	73.2 ± 6.8	123.1 ± 10.0	89.3 ± 10.0	122.0 ± 7.3	180.1 ± 19.8	147.3 ± 2.1
V_{max}	1257 ± 23	590.2 ± 14.1	247.7 ± 5.6	107.1 ± 2.6	428.1 ± 12.7	219.2 ± 3.9	315.9 ± 11.8	152.6 ± 7.3
V_{max}/K_m	12.33	5.35	3.38	0.86	4.79	1.79	1.75	1.03
Tryptamine K_m	13.1 ± 0.9	36.5 ± 5.1	5.0 ± 0.4	98.0 ± 19.2	13.9 ± 0.7	198.9 ± 17.7	11.9 ± 2.3	176.4 ± 10.4
V_{max}	370.7 ± 6.3	51.7 ± 1.4	59.3 ± 1.4	59.7 ± 3.2	87.1 ± 1.9	100.3 ± 3.1	56.4 ± 4.1	52.8 ± 1.1
V_{max}/K_m	28.38	1.41	11.83	0.60	6.27	0.50	4.73	0.29
Dopamine K_m	109.6 ± 8.3	1892 ± 83	271.6 ± 16.9	861 ± 93	146.8 ± 22.2	1150 ± 92	196.7 ± 16.9	404.6 ± 70.5
V_{max}	1132 ± 25	1607 ± 5	568.2 ± 20.6	1597 ± 101	800.0 ± 38.7	1158 ± 86	398.0 ± 18.1	736.4 ± 21.4
V_{max}/K_m	10.33	0.84	2.16	1.85	5.44	1.01	2.02	1.82
5-HT K_m	107.5 ± 6.8	—	112.2 ± 7.6	—	170.5 ± 0.3	—	140.7 ± 18.0	—
V_{max}	789.5 ± 14.3	—	355.7 ± 68.0	—	465.6 ± 0.3	—	198.7 ± 8.0	—
V_{max}/K_m	7.37	—	3.01	—	2.73	—	1.41	—
PEA K_m	—	4.8 ± 0.8	—	4.9 ± 0.9	—	4.4 ± 0.9	—	4.7 ± 0.7
V_{max}	—	91.9 ± 3.6	—	92.7 ± 7.1	—	112.2 ± 5.4	—	66.9 ± 2.3
V_{max}/K_m	—	19.14	—	18.9	—	25.45	—	14.25

Values were determined from initial rate data obtained at 37° by the procedures described in the text. The concentration range used was 5–50 μM for PEA, 12.5–100 μM for tryptamine in the case of MAO A, 50 μM–5 mM for dopamine in the case of MAO B and 50 μM–2 mM in all other cases. K_m and V_{max} values are expressed in μM and pmol/min/mg protein, respectively.

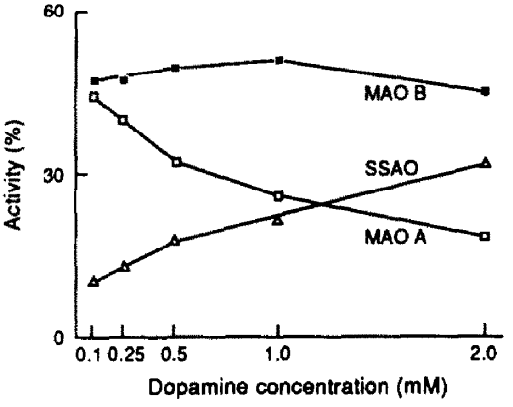

Fig. 4. Contributions of MAO A, MAO B and SSAO activities from bovine retina to dopamine oxidation. The curves were calculated from the kinetic parameters shown in Table 3.

The inhibition curves clorgyline, in which the remaining activity towards different substrates was measured, showed that in all the tissues tyramine, tryptamine and dopamine were metabolized by both MAO forms. In the retina and choroid, a remnant activity (10%) was observed that was resistant to inhibition by 1 mM clorgyline, indicating the presence of a SSAO activity that was responsible for its deamination. Serotonin and PEA were metabolized exclusively by MAO A and MAO B, respectively, in all cases. At 1 mM clorgyline it was observed in all the tissues that about 30–40% of the total activity towards benzylamine was resistant to inhibition. This indicates that SSAO activity was responsible for part of the benzylamine deamination in all the eye tissues.

Although the central nervous system and retina have the same embryonic origin [16], SSAO activity is present in the retina but is apparently absent from brain [17, 18].

The distribution of different kinds of activity, taken from the inhibition curves, showed MAO A, MAO B and SSAO to all be present in the different parts of the bovine eye, contributing to different extents to amine metabolism depending on the nature of the substrate used and its concentration. These values are, however, only approximate because they were determined at only one fixed substrate concentration.

The contribution to the metabolism of each substrate by both forms of MAO will depend on the substrate concentration and the V_{max}/K_m ratio. Except for PEA, which was metabolized exclusively by MAO B and serotonin which was metabolized by MAO A in all tissues, the rest of the substrates were metabolized mainly by MAO A as can be deduced from the V_{max}/K_m ratio (Table 3). This is in agreement with the data obtained from the inhibition curves. Dopamine is metabolized by both MAO A and B, the relative contributions depending on the substrate concentration used. It has been reported recently that this amine can also be deaminated by SSAO present in rat vas deferens [11]. The present work shows that SSAO can also contribute, to an extent depending on the substrate concentration, to the deamination of dopamine in the retina and choroid, but not in the iris or optic nerve. The absence of detectable SSAO activity towards dopamine in the latter two tissues contrasts to the presence of this enzyme when benzylamine was used as substrate. The term SSAO covers a wide variety of amine oxidases with different substrate specificities (see Ref. 19) and not all of these are active towards dopamine. The observed differences between the different tissues of the eye might suggest that they contain different forms of SSAO. Although the kinetic parameters suggest that SSAO activity may play a role in the metabolism of dopamine in the retina, which contains relatively high concentrations of this neurotransmitter amine [20], further studies on the localization of the different enzymes would be necessary before its importance could be fully assessed.

The absence of SSAO activity towards dopamine in the optic nerve but its presence in the choroid and retina might suggest it to be associated with capillaries. This would be consistent with the known association of this enzyme with vascularized tissues and, perhaps, support the suggestions by Favard *et al.* [9] that the capillaries might play an important role in controlling the dopamine levels in the retinal compartment.

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