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EFFECTS OF MONOAMINE OXIDASE INHIBITORS ON THE ACID METABOLITES OF SOME TRACE AMINES AND OF DOPAMINE IN THE RAT STRIATUM

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Abstract—The effects of the administration of selective and non-selective inhibitors of monoamine oxidase (MAO) on the concentrations of three trace acid metabolites [phenylacetic acid (PAA); *m*-hydroxyphenylacetic acid (mHPAA); and *p*-hydroxyphenylacetic acid (pHPAA)] and of an acid metabolite of dopamine [3,4-dihydroxyphenylacetic acid (DOPAC)] in the rat striatum were determined. Administration of brofaromine (1–100 mg/kg, s.c.) a type A MAO inhibitor, dose-dependently decreased DOPAC and mHPAA levels. pHPAA levels were decreased by 100 mg/kg brofaromine, but PAA levels were unaffected. Doses of deprenyl of less than 100 mg/kg, i.p., had no effect on any of the acids, while 100 mg/kg decreased DOPAC, mHPAA and pHPAA but not PAA levels. Clorgyline, pargyline and tranylcypromine treatment decreased the levels of DOPAC, mHPAA and pHPAA but not PAA. Administration of α-monofluoromethyldopa, an inhibitor of aromatic amino acid decarboxylase, decreased the levels of all four acids. It was concluded that deamination of the respective parent amine by type A MAO is primarily responsible for the synthesis of DOPAC and mHPAA, but that another pathway contributes to pHPAA synthesis. It appears that either PAA arises predominantly independently from the actions of MAO or that its removal via transport or further metabolism regulates its concentration.

It has been shown that some of the trace amines are selective endogenous substrates for either type A or type B monoamine oxidase (MAO†; amine:oxygen oxidoreductase [deaminating] [flavin-containing], E.C. 1.4.3.4) within the rat striatum [1, 2]. Thus, phenylethylamine present in the rat striatum is deaminated preferentially by type B MAO, while *m*- and *p*-tyramine in the rat striatum are metabolized preferentially by type A MAO [1, 2]. Increases in the striatal levels of phenylethylamine, *m*-tyramine and *p*-tyramine can thus be used as a method to assess the *in vivo* specificity of MAO inhibitors.

Since deamination of phenylethylamine, *m*-tyramine and *p*-tyramine is a major pathway and since deamination of these amines in the rat striatum is catalysed by a specific isozyme of MAO (type A or B), decreases in the acid metabolites of these MAO-selective trace amines should reflect which type of MAO has been inhibited. Since phenylethylamine is a type B MAO substrate in the rat striatum, inhibitors of type B MAO should decrease the levels of phenylacetic acid (PAA). Similarly, since endogenous *m*- and *p*-tyramine in the rat striatum are type A MAO substrates, type A MAO inhibitors should decrease the levels of *m*-hydroxyphenylacetic acid (mHPAA) and *p*-hydroxyphenylacetic acid (pHPAA) in the rat striatum. In the following study, therefore, the effects of specific and non-selective inhibitors of MAO on the levels of these three acid metabolites were determined. In addition, the effects of these drugs on the levels of the acid metabolite of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), were determined for comparative purposes.

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† Abbreviations: MAO, monoamine oxidase; PAA, phenylacetic acid; mHPAA, *m*-hydroxyphenylacetic acid; pHPAA, *p*-hydroxyphenylacetic acid; DOPAC, 3,4-dihydroxyphenylacetic acid; AAD, aromatic-L-amino-acid decarboxylase; TFE, trifluoroethyl ester; TFE-PFP, trifluoroethyl ester-*O*-pentafluoropropionate; and MFMD, α-monofluoromethyldopa.

MATERIALS AND METHODS

Materials

Water was purified by reverse osmosis (Barnsted ROpure) followed by ion exchange and carbon and colloid filtration (Barnsted Nanopore II). This Nanopure (18 megohm) water was then glass distilled from alkaline potassium permanganate to remove traces of oxidizable compounds.

Reagents were obtained as follows: 5-sulfosalicylic acid (Aristar), sodium hydroxide (ACS assured), anhydrous sodium chloride (ACS assured), potassium permanganate, and potassium dihydrogen phosphate (ACS assured) from B.D.H. Inc., Toronto, Ontario, Canada; triethylamine (Baker analysed) from J.T. Baker, Hayward, CA; EDTA and sodium *m*-bisulfite, trifluoroethanol and pentafluoropropionic anhydride from Aldrich, Milwaukee, WI, U.S.A.; benzene (Fisher Spectranalysed) from Fisher Scientific, Edmonton, AB, Canada; and hexane and ethyl acetate (HPLC grade) from Caledon, Georgetown, Ontario, Canada.

The deuterated internal standards phenylacetic

acid-ring-d_5 (PAA-d_5), *m*-hydroxyphenylacetic acid-d_4 (mHPAA-d_4), *p*-hydroxyphenylacetic acid-d_4 (pHPAA-d_4) and 3,4-dihydroxyphenylacetic acid-d_5 (DOPAC-d_5) were prepared in this laboratory by B. A. Davis. The non-deuterated standards PAA, mHPAA and pHPAA, and DOPAC were obtained from Aldrich or Sigma, St. Louis, MO, U.S.A. The drugs used and their suppliers were as follows: brofaromine (CGP 113 05 A) (Ciba-Geigy Canada Ltd.); tranylcypromine HCl, pargyline HCl, clorgyline HCl (Sigma); L-deprenyl HCl (Research Biochemicals Inc.) and α-monofluoromethyldopa (MFMD) (Merrell Dow).

Treatment of animals

Male Wistar rats (body wt 200–250 g) were purchased from Charles River Canada (Montreal, P. Q.) and housed in hanging wire cages with free access to food and water. They were injected subcutaneously or intraperitoneally with saline or with one of the drugs listed above dissolved in saline. Treatment time was 4 hr. After this, the rats were killed by stunning, cervical dislocation and removal of the brain. The brains were immersed in ice-cold saline, and the corpus striata dissected out on ice-chilled Petri dishes. Corpus striata from one rat were pooled, frozen on dry ice and stored at −70° for 1–3 days before analysis.

Measurement of PAA, mHPAA, pHPAA and DOPAC

The analytical procedure was a modification of those previously reported [3–5] in which a number of acids, including PAA, mHPAA, pHPAA and DOPAC, were quantitated after derivatization: the trifluoroethyl ester (TFE) derivative for PAA and the trifluoroethyl ester-*O*-pentafluoropropionate (TFE-PFP) derivative for mHPAA, pHPAA and DOPAC.

Extraction and derivatization. Tissues were homogenized in 1.5-mL microcentrifuge tubes with a Kontes disposable polypropylene pestle and a Kontes pellet pestle motor with 1 mL of a solution of 6% sulfosalicylic acid containing deuterated internal standards (50 ng each of PAA-d_5, mHPAAd_4 and pHPAA-d_4; and 100 ng of DOPAC-d_5), 0.2% EDTA and 0.1% sodium bisulfite. The tubes were centrifuged at 10,000 *g* for 15 min and the supernatant was transferred to a new test tube, saturated with NaCl and extracted three times with 2 mL ethyl acetate. The organic phase was reduced in volume under a stream of nitrogen, benzene (1 mL) was added, and the volume reduced to 0.5 mL. The solution was then transferred to a Reactivial (Pierce), 100 μL of 1% triethylamine in benzene was added, and the volume was carefully reduced just to dryness. Pentafluoropropionic anhydride (PFPA, 50 μL) and trifluoroethanol (50 μL) were added and reacted for 1 hr at 80° C. The vials were cooled, the volume was reduced to 50 μL, another aliquot of PFPA was added and the reaction repeated for another 1 hr. Again the vials were cooled, 200 μL of hexane was added and the solution shaken with 100 μL phosphate buffer (pH 6.0) for about 30 sec. The hexane layer was transferred to a microvial (11 mm autoinjector vial with a 100 μL vial liner), the volume was reduced to about 25 μL under the nitrogen stream, and the vials were capped. Each batch of tissue samples was accompanied by blanks (no tissue) and checks (known amounts of protio acids: 2.5 to 50 ng for PAA, mHPAA and pHPAA and 5 to 100 ng for DOPAC).

GC–MS analyses. Gas chromatographic–mass spectrometric analyses were undertaken using an MS902S (Kratos) mass spectrometer with VG electronics operated at 5000 resolution in the selected ion monitoring mode and an HP 5700 GC with capillary injector. The column, an SPB1 60 m × 0.32 mm i.d. fused silica capillary column, 1 μm film (Supelco), was connected to the GC inlet via a 1 m length of deactivated fused silica (0.53 mm i.d.) and to the ion source via a pseudo open split interface and a 1 m length of 0.200 mm i.d. fused silica. The carrier gas was helium and the GC program was 110° for 4 min, 10°/min to 180°, 24° to 290° and then 4 min isothermal. One microliter of each sample was injected and the following ions were monitored: *m/z* 218.055, TFE-PAA; 223.0868, TFE-PAA-d_5; *m/z* 380.0297, TFE-PFP-m- and TFE-PFP-pHPAA; 384.0548, TFE-PFP-m- and TFE-PFP-pHPAA-d_4; *m/z* 542.0035, TFE-$(PFP)_2$-DOPAC; and *m/z* 547.0349, TFE-$(PFP)_2$-DOPAC-d_5.

Statistical analyses

The effects of brofaromine (1 to 100 mg/kg) or of deprenyl (0.1 to 100 mg/kg) on the levels of PAA, mHPAA, pHPAA or DOPAC in the rat striatum were analysed by one-way analysis of variance followed by tests for significant differences from saline using Scheffe's test [6]. The effects of other inhibitors of MAO or of α-monofluoromethyldopa on the levels of these acids were assessed in the same manner.

RESULTS

Effects of brofaromine on acid levels in the rat striatum

Doses of brofaromine equal to or greater than 1 mg/kg dose-dependently decreased DOPAC levels in the rat striatum (Fig. 1). mHPAA levels were affected by administration of brofaromine in the same manner, but the maximum reduction was smaller (to 44% of saline treatment) compared to DOPAC (to 11%). Brofaromine administration, by contrast, had little effect on striatal pHPAA levels. No reduction was observed with 1 and 10 mg/kg brofaromine, while the 100 mg/kg dose reduced pHPAA to 56% of control. PAA levels in the rat striatum were not decreased by any of the doses of brofaromine used.

Effects of deprenyl on acid levels in the rat striatum

Administration of deprenyl to rats had little or no effect on the concentrations of the selected acid metabolites in the rat striatum (Fig. 2). Doses of deprenyl of less than 100 mg/kg did not reduce significantly the levels of any of the four acids analysed. Significant decreases in striatal DOPAC, mHPAA and pHPAA levels were observed following 100 mg/kg deprenyl treatment of the rats, but no

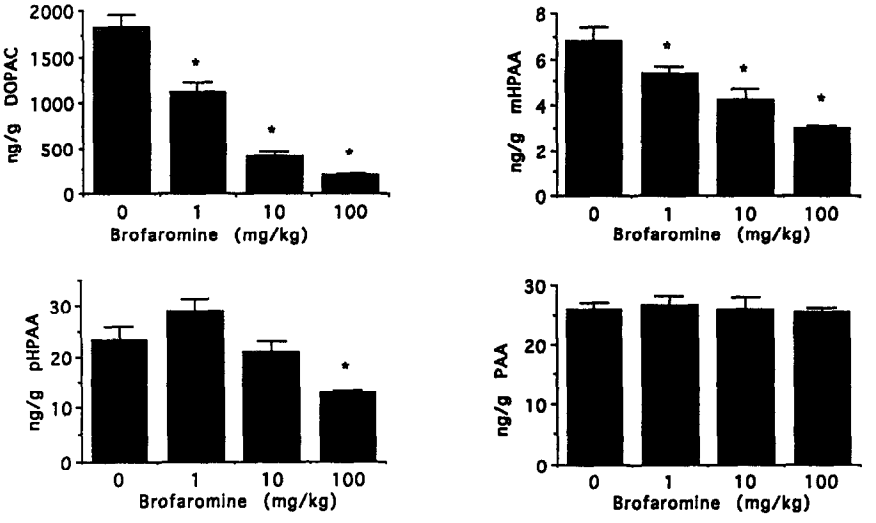

Fig. 1. Effects of subcutaneously administered brofaromine on the concentrations of DOPAC (3,4-dihydroxyphenylacetic acid), mHPAA (*m*-hydroxyphenylacetic acid), pHPAA (*p*-hydroxyphenylacetic acid) and PAA (phenylacetic acid) in the rat striatum 4 hr after injection. Concentrations of each acid are nanograms acid per gram of wet tissue (mean ± SEM, N = 5–8). An asterisk indicates that the value was significantly different from the respective saline control at the 5% probability level.

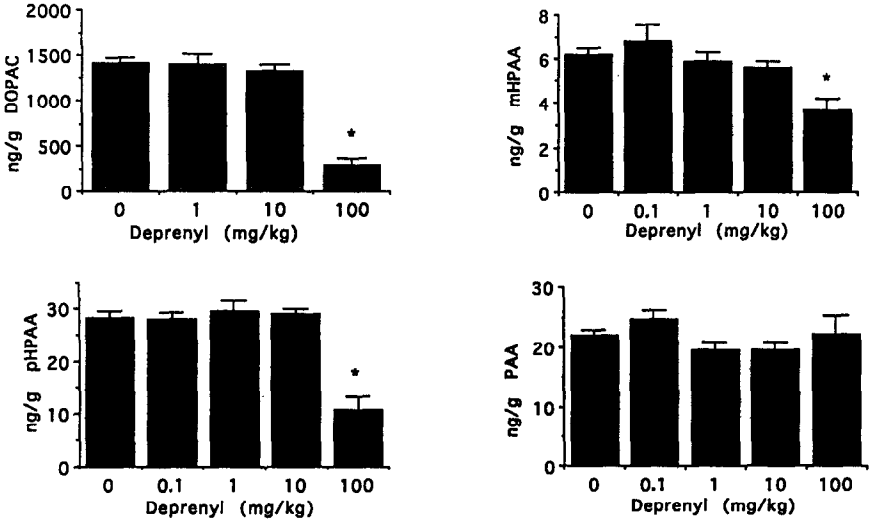

Fig. 2. Effects of intraperitoneally administered deprenyl on the concentrations of DOPAC (3,4-dihydroxyphenylacetic acid), mHPAA (*m*-hydroxyphenylacetic acid), pHPAA (*p*-hydroxyphenylacetic acid) and PAA (phenylacetic acid) in the rat striatum 4 hr after injection. Concentrations of each acid are nanograms acid per gram of wet tissue (mean ± SEM, N = 8–14). An asterisk indicates that the value was significantly different from the respective saline control at the 5% probability level.

decrease in PAA was found. The decrease in DOPAC (to 21% of control) was greater than that for mHPAA and pHPAA (to 60 and 39%, respectively).

Effects of other MAO inhibitors and α-monofluoromethyldopa on striatal acid levels

Other inhibitors of MAO were injected into rats at doses that have been shown to increase the levels of phenylethylamine, *m*- and *p*-tyramine in the striatum [1]. Clorgyline, an irreversible type A MAO inhibitor, failed to reduce PAA levels, but decreased the levels of mHPAA, pHPAA and DOPAC significantly (Table 1). The levels of m- and pHPAA were reduced to 72–73% of control, while DOPAC levels were reduced to 35% of control. Non-

Table 1. Effects of other MAO inhibitors and α-monofluoromethyldopa on acid metabolite levels in the rat striatum

	PAA (ng/g)	mHPAA (ng/g)	pHPAA (ng/g)	DOPAC (ng/g)
Saline (16)	23.8 ± 1.2	6.1 ± 0.3	28.5 ± 1.3	1591 ± 54
Clorgyline (10)	27.3 ± 0.9	4.1 ± 0.5*	17.9 ± 1.9*	573 ± 185*
Tranylcypromine (11)	20.1 ± 3.2	0.6 ± 0.2*	3.7 ± 0.5*	20 ± 6*
Pargyline (5)	18.1 ± 1.3	0.4 ± 0.2*	6.0 ± 0.8*	25 ± 8*
MFMD (6)	10.1 ± 1.1*	1.2 ± 0.4*	3.9 ± 0.4*	445 ± 37*

Values are ng of amine/g tissue wt, mean ± SEM, with sample size shown in parentheses. Rats were injected with 0.9% saline (i.p.), tranylcypromine (s.c., 10 mg/kg), clorgyline (i.p., 5 mg/kg), pargyline (i.p., 100 mg/kg) or MFMD (α-monofluoromethyldopa) (i.p., 100 mg/kg), and 4 hr later measurements were made.

* $P < 0.05$ compared to saline.

selective inhibition of MAO by tranylcypromine administration did not decrease PAA levels, but did decrease mHPAA, pHPAA and DOPAC levels to 10, 13 and 1% of control, respectively. Similarly, pargyline treatment failed to reduce PAA levels, but decreased mHPAA, pHPAA and DOPAC to 6, 18 and 2% of control, respectively. α-Monofluoromethyldopa, an inhibitor of aromatic-L-amino-acid decarboxylase (AAD), injected at a centrally active dose [7], decreased the levels of the four acid metabolites. PAA levels fell to 51%, mHPAA to 17%, pHPAA to 12% and DOPAC to 27% of their respective control levels.

DISCUSSION

The deamination of a given biogenic amine by type A or B MAO depends not only on its substrate affinity for the particular isozyme, but also on the cellular and subcellular localization of the isozymes and of the amine. In the rat striatum, MAO A is present predominantly in nerve terminals while MAO B is located in glial cells [8, 9]. Dopamine released from the nerve terminals is recaptured by a high affinity uptake process and, thus, dopamine in the rat striatum is deaminated predominantly by type A MAO [10–14].

Deprenyl is a type B monoamine oxidase inhibitor [15], while clorgyline and brofaromine are irreversible and reversible inhibitors of MAO A, respectively [16–19]. It has been shown that DOPAC levels in the rat striatum are decreased by selective inhibition of MAO A with clorgyline or brofaromine but not by selective inhibition of MAO B with deprenyl [10–14, 20]. The results presented here are in agreement. Clorgyline treatment decreased striatal DOPAC levels (Table 1), and only the 100 mg/kg dose of deprenyl, a non-selective dose [21], decreased DOPAC levels. As observed previously [20], injection of brofaromine into rats led to a dose-dependent decrease in striatal DOPAC levels (Fig. 1).

Like dopamine, *p*-tyramine and *m*-tyramine released from nerve terminals in the rat striatum can be retrieved by high affinity re-uptake [22]; thus, these amines may also be preferentially exposed to MAO A in the nerve terminals rather than to glial MAO B. Since phenylethylamine is neither stored nor actively transported into nerve terminals [23, 24], it is likely that it can be deaminated by both neuronal MAO A and glial MAO B.

It has been concluded that striatal *m*-tyramine is deaminated primarily by type A MAO [2]. The present findings support this conclusion. Administration of low (type B selective) doses of deprenyl did not decrease the levels of mHPAA, the acid metabolite of *m*-tyramine (Fig. 2). By contrast, brofaromine dose-dependently decreased mHPAA levels (Fig. 1); clorgyline also decreased mHPAA (Table 1). Injection of the non-selective MAO inhibitors decreased mHPAA more than the MAO A inhibitors (Table 1). There are no previous reports regarding the effects of MAO inhibitors on mHPAA in the rat striatum; mouse striatal mHPAA is decreased by non-selective inhibition of MAO with pargyline [22].

The few papers describing the effects of MAO inhibitors on the acid metabolite of *p*-tyramine in rodent brain are somewhat inconsistent. In the mouse, pargyline administration causes a reduction in striatal pHPAA levels [25]. In the rabbit and rat brain, by contrast, neither mixed nor selective MAO inhibitors decrease pHPAA levels [26, 27]. Neither selective inhibition of type A MAO by low doses of brofaromine nor selective inhibition of type B MAO with low doses of deprenyl decreased striatal pHPAA levels (Figs. 1 and 2). Inhibition of MAO A by administration of 5 mg/kg clorgyline did decrease pHPAA levels to 72% of control (Table 1). This dose of clorgyline has been reported to be selective [28]. The present findings show that type B MAO is probably not important in the formation of pHPAA, and that while some pHPAA may arise via the actions of type A MAO, this may not be its major route of biosynthesis. There may be an alternate source of pHPAA, such as synthesis through transamination of *p*-tyrosine and subsequent oxidative decarboxylation of *p*-hydroxyphenylpyruvic acid, as has been suggested previously [27, 29].

Neither deprenyl nor the other MAO inhibitors reduced striatal PAA levels (Figs. 1 and 2, Table 1). It is difficult to reconcile this finding with that of the increased striatal phenylethylamine levels after

administration of deprenyl or non-selective MAO inhibitors [1, 2]. According to the following metabolic scheme, inhibition of MAO by deprenyl which increases phenylethylamine levels should be accompanied with decreased PAA levels:

phenylalanine ⇒ phenylethylamine ⇒ phenylacetaldehyde ⇒ PAA
(AAD) (MAO) (aldehyde dehydrogenase)

Furthermore, it is not clear why blocking the synthesis of PAA at two different points in this pathway had different effects. Inhibition of MAO failed to decrease PAA levels, and yet inhibition of AAD with α-monofluoromethyldopa did reduce PAA levels. Such anomalous results were not found with the other acids (Figs. 1 and 2, Table 1); the levels of mHPAA, pHPAA and DOPAC were decreased significantly by inhibitors of MAO and AAD.

No previous work has been published on the effects of MAO inhibitors on rat striatal levels of PAA, although it has been reported that PAA levels in the rabbit brain are decreased by deprenyl, pargyline and α-methyldopa treatments [26]. The discrepancy between these and the present findings may be due to differences in the species studied, the analytical methods used, or differences between whole brain versus regions of the brain.

The observed lack of effect of MAO inhibitors on PAA levels in the rat striatum may be explained by at least three possibilities. First, there may be more than one metabolic source of PAA and deamination of phenylethylamine may not be the major one. Second, shutting down the synthesis of PAA from phenylethylamine by inhibition of MAO may be accompanied by an increased synthesis of PAA from an alternate source. It has been suggested previously that human urinary PAA originates mainly via a transamination pathway as follows [30]:

phenylalanine ⇒ phenylpyruvic acid ⇒ PAA
(transamination) (oxidative decarboxylation)

Finally, it may be that the significant factor regulating PAA levels is not its synthesis but rather its removal from the striatum by transport out of the striatum or conversion into another metabolite, such as a conjugate. Not much is known about the formation of conjugates of trace acid metabolites in humans or in rats. According to a review [31], most (51–94% of the total) PAA in human body fluids exists as a conjugate, while much less (14–24%) pHPAA and mHPAA is conjugated. Almost all (93%) of the PAA in rat urine is conjugated [32]. No information is available on the conjugation of PAA in the rat brain; in the rabbit brain it has been claimed that there is no conjugation [26]. A small proportion of mouse striatal pHPAA is conjugated, but mHPAA is not conjugated [33]. The available data, with the exception of the report concerning the rabbit brain, suggest that conjugation plays a more significant role in the disposition of PAA than the other acids.

If most of the PAA in the rat striatum is conjugated, this rather than its synthesis, may be the rate-limiting step which determines free (unconjugated) PAA concentrations. It is pertinent to note that the concentration of free PAA in rat urine is not decreased by administration of a non-selective MAO inhibitor to rats, but that there appears to be a decrease in the amounts of conjugated PAA [32]. Studies are currently underway to determine whether PAA in the rat striatum is conjugated, and, if so, what is the nature of the conjugate and what proportion of the total PAA is conjugated.

Because α-monofluoromethyldopa a specific AAD inhibitor with little or no inhibition of tyrosine transaminase [34–36] decreased the levels of PAA, mHPAA, pHPAA and DOPAC, it can be concluded that a portion of these acids arose from the pathway involving synthesis of the respective parent amines. Judging by the percentage decreases caused by treatment with this AAD inhibitor, this seems to be a major pathway of formation of mHPAA and pHPAA, and perhaps DOPAC, but it appears to be less important for PAA.

In summary, the effects of deprenyl, brofaromine and clorgyline on the levels of several acid metabolites in the rat striatum support the notion that dopamine and *m*-tyramine are deaminated preferentially by type A MAO. The effects of these selective and other non-selective MAO inhibitors on the levels of pHPAA in the rat striatum suggest that *p*-tyramine is deaminated by the actions of both types of MAO. None of the selective or non-selective MAO inhibitors reduced PAA in the rat striatum; thus, PAA levels do not reflect the activity of MAO in the rat striatum. It appears that either the major route of PAA synthesis occurs via a pathway not involving MAO or that removal of PAA from the striatum is the factor controlling its levels.

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