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Cerebral decarboxylation of *meta*- and *para*-tyrosine

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Summary. The decarboxylase inhibitor DL-*a*-monofluoromethyldopa reduces, in a dose dependent manner, the concentration of striatal *p*-tyramine in the mouse. Homovanillic acid is also significantly reduced. Conversely, this treatment increases the *m*-tyramine concentration. Administration of *m*-tyrosine produces large increases in *m*-tyramine and a slight decrease in *p*-tyramine; these changes are potentiated in the presence of the decarboxylase inhibitor. Such data along with other recently published results permit the conclusion that *m*-tyramine arises from phenylalanine via *m*-tyrosine and that *p*-tyramine arises by decarboxylation of *p*-tyrosine. Both these reactions are closely related to the activity of tyrosine hydroxylase and the availability of appropriate substrates.

The formation of the putative neurotransmitters dopamine (DA) and 5-hydroxytryptamine (5-HT) is via decarboxylation of their respective hydroxylated precursor amino acids, DOPA and 5-hydroxytryptophan[4,7,78]. These particular amines are concentrated in quite significant amounts (i.e. µg/g quantities) in parts of the mammalian brain (basal ganglia, mesolimbic system, hypothalamus, etc.)[2,5]. The enzyme responsible for their formation, aromatic L-amino acid carboxylyase (EC 4.1.1.28) is fairly ubiquitously distributed, although there is some doubt as to whether it is a single protein[72,73].

We have been interested for some time in a related group of biogenic amines that have been dubbed erroneously the trace amines because of their tiny tissue concentrations (low ng/g)[9,11,20]. By employing fairly sophisticated mass spectrometric techniques it has proved possible to identify and quantitate several of these trace amines, *β*-phenylethylamine (PE)[35], tryptamine (T)[66] and *meta*- and *para*-tyramine (mTA and pTA)[65,67] and to demonstrate their heterogenous distribution throughout the brain[21,35,51,65-68] and within the cell[13,14].

There seems little doubt that PE and T are formed directly by decarboxylation of phenylalanine and tryptophan respectively[29,61]. The case for the TA's is more complex since *meta*-tyrosine has not hitherto been thought to be a normal tissue component, *para*-tyrosine decarboxylation appears to be very slow[43] and both mTA and pTA can be formed by hydroxylation of PE[15,18,30,38] and dehydroxylation of dopa and dopamine[15,25-27,38] both peripherally and centrally.

Despite their tiny concentrations, however, these biogenic trace amines are interesting because they exhibit very fast turnover rates[21,34,64,75,76], increase differentially and markedly their tissue and body fluid levels after monoamine oxidase blockade[64] and their deaminated catabolites, phenylacetic acid, indoleace-

tic acid and *meta*- and *para*-hydroxyphenylacetic acid, are present, in urine, in large amounts. In addition the tyramines have been shown to be depleted by releasing agents in a manner that is similar to that of the catecholamines (CA's) and 5-HT[22,54]; are concentrated by high and low affinity transport systems[36,62,63]; are released both in vitro and in vivo by the usual depolarizing agents and certain stimulant drugs[16,17,36,37,39-41]; behave in an inhibitory manner when iontophoresed at conventional current levels onto cortical or caudate neurones[45] but act as specific potentiators of the CA's and 5-HT when iontophoresed at low current levels[46-50]; are behaviorally active[42] and are related, both directly and indirectly, to particular components of behavior[32,33] when injected i.p.; and they appear to be involved in the aetiology of schizophrenia[24,28,31,69,77], Parkinsonism[23,74], hepatic coma[44], the affective disorders[71] and aggression[16,70].

Striatal pTA and mTA are reciprocally related to DA turnover and this relationship has been confirmed in the presence of DA agonists, antagonists, releasors, synthesis blockers, precursors, appropriate lesions and stress (table 1). Such findings led us to investigate further the relationships between DA synthesis and turnover and the synthesis of the TA's, particularly the effect of suitable precursor amino acids and decarboxylase inhibitors[59]. In this paper we describe the effects of α-monofluoromethyldopa (FMD)[6] on the levels of striatal pTA and mTA and homovanillic acid in the mouse. In addition, the effect of the precursor *m*-tyrosine is also assessed.

Materials and methods

Male albino Swiss mice (18-22 g b.wt) were killed by decapitation, the brain was removed rapidly and the striatum, consisting mainly of the head of the caudate nucleus and including some of the underlying putamen (approximate weights were between 25 and 35 mg), was dissected out. Striata from 3 mice were pooled, immediately frozen in dry ice, weighed and homogenized in 0.1 N HCl containing disodium edetate (EDTA, 1 mg/ml). The amines in the tissue homogenate were derivatized directly with 5-dimethylamino-1-naphthalene sulphonyl (dansyl) chloride and the resultant derivatives extracted into a toluene-ethylacetate (9:1) mixture, evaporated to a small volume, separated chromatographically and estimated by the high resolution mass spectrometric selected ion monitoring (integrated ion current) technique using deuterated *p*- or *m*-tyramine as internal standards. Complete details concerning this procedure have been described[65,66]. In order to avoid using benzene and chloroform, which are toxic and hazardous to use in the laboratory, the solvent systems have been recently modified[57].

Homovanillic acid was estimated using the pooled striata of 5 mice; the tissues were homogenized in 0.1 N HCl, deproteinized with 0.4 N perchloric acid, extracted with n-butylacetate and from it into 0.05 M tris buffer, and estimated fluorimetrically[3]. Checks on the recovery of added homovanillic acid (200 ng) were carried out in every experiment; the percentage of recovery was 82 ± 4^6 (mean ±SEM); number of experiments in brackets and the results were corrected accordingly.

DL-α-Monofluoromethyldopa (RMI 71963) was generously supplied by Centre de Recherche, Merrel International, Strasbourg, France. The drug was dis-

Table 1. Relation between changes in brain dopamine turnover with *p*-tyramine and *m*-tyramine concentrations. The superscript indicate the source of reference

1. Dopamine turnover increase, *p*-tyramine reduction, *m*-tyramine no change or increase
   - a Dopamine receptor blockers, chlorpromazine[52], thioridazine[19], thioproperazine[19], fluphenazine[56], α-fluphenthixol[52], (+)-butaclamol[52], molindone at low doses[56], spiperone[54].
   - b Dopamine releasors and uptake blockers - d-amphetamine[53].
   - c Short term (up to 24 h) lesion of the pars compacta of the substantia nigra[60], or administration of γ-hydroxybutyrate[57].
   - d Stress[55].
2. Dopamine turnover reduction, *p*-tyramine increase, *m*-tyramine no change or reduction
   - a Direct inhibition of tyrosine hydroxylase, α-methyl-p-tyrosine[54]. Indirect inhibition of tyrosine hydroxylase, apomorphine[54], lergotrile[54], piribedil[54], molindone at high doses[56].

Table 2. Effects of the s.c. administration of α-fluoromethyldopa on mouse striatal *p*-tyramine (pTA), *m*-tyramine (mTA) and homovanillic acid (HVA)

Dose mg/kg	Time h	pTA ng/g	mTA ng/g	HVA ng/g
–	–	24.2 ± 1.1 (14)	6.8 ± 0.5 (14)	820 ± 60 (5)
0.1	6	20.5 ± 1.7 (4)	8.7 ± 0.7 (4)[a]	–
1	3-6	16.3 ± 1.1 (4)[c]	16.4 ± 1.2 (4)[c]	–
10	3	14.7 ± 2.3 (9)[b]	21.7 ± 0.7 (9)[c]	–
10	6	15.8 ± 1.5 (8)[c]	23.9 ± 1.1 (8)[c]	–
50	3	4.2 ± 0.6 (9)[c]	16.3 ± 1.2 (9)[c]	640 ± 40 (9)[a]
50	6	1.1 ± 0.3 (7)[c]	10.2 ± 1.8 (7)	530 ± 50 (6)[b]
100	3	2.0 ± 0.1 (4)[c]	10.2 ± 1.2 (4)[b]	–

Values are means (± SEM, number of experiments in parentheses) in ng/g of fresh tissue. Student's t-test [a]$p < 0.05$; [b]$p < 0.005$; [c]$p < 0.001$.

Table 3. Effects of the administration of α-fluoromethyldopa (FMD) and *m*-tyrosine (*m*-Tyr) on mouse striatal *p*- and *m*-isomers of tyramine (pTA or mTA)

	Dose mg/kg	Time h	*p*-TA ng/g	*m*-TA ng/g
Controls	–	–	24.2 ± 1.1 (14)	6.8 ± 0.5 (14)
FMD	50	3	4.2 ± 0.6 (9)[b]	16.3 ± 1.2 (9)[b]
m-Tyr	2	2	20.8 ± 0.7 (3)[a]	97.5 ± 5.9 (3)[b]
FMD+	50	3		
m-Tyr	2	2	7.8 ± 1.8 (4)[b]	413.7 ± 32.3 (4)[b]

Values are means (± SEM, number of experiments in parentheses) in ng/g of fresh tissue. The mice treated with FMD and *m*-Tyr were first given FMD, 1 h later m-Tyr, and killed 3 h after the beginning of the experiment. Student's t-test: [a]$p < 0.025$; [b]$p < 0.001$. The t-values were obtained by comparison with those groups of mice treated with *m*-tyrosine or α-fluoromethyldopa.

solved in saline and injected s.c. DL-*m*-Tyrosine (Sigma, St. Louis, Missouri, USA) was suspended in saline containing 2.2 mg/ml of Tween 80.

Results

Previous studies[59] have shown that the central decarboxylase inhibitor NSD 1055 produced the expected decrease in the formation of pTA but surprisingly an increase in the amount of mTA. After L-phenylalanine (PA) both amines increased but when PA was given with NSD 1055, a further significant increase was found in the amount of mTA while the pTA was again decreased. After a dose of *p*-tyrosine, pTA increased and mTA decreased; both were decreased when the *p*-tyrosine was given along with NSD 1055 although the further reduction from the *p*-tyrosine treatment alone in the case of mTA was not significant. After a dose of *m*-tyrosine, as would be expected, mTA increased; when the treatment included the decarboxylase inhibitor, mTA increased further. PTA was decreased by both of these treatments.

The s.c. administration of FMD (1 mg/kg) produced a reduction in the concentration of mouse striatal pTA to 67% of the controls that became evident 3 or 6 h later (which is the usual time of maximal increase in the trace amines following monoamine oxidase blockade[64]). The effect was dose-dependent so that at 100 mg/kg the pTA level was reduced to 5-8% of the control value (table 2). Simultaneously this treatment increased striatal mTA concentrations (table 2) and significant increases were observed with doses as low as 0.1 mg/kg (i.e. to 128% of controls). The maximal increase was observed at 6 h with a dose of 10 mg/kg (to 352% of controls) but significant increases were observed at the higher doses (50-100 mg/kg), although these increases were less than those seen at 3 or 6 h after 10 mg/kg.

The mouse striatal concentration of homovanillic acid was reduced (to 65-78% of controls 3-6 h after FMD administration (50 mg/kg) (table 2).

The s.c. administration of *m*-tyrosine (2 mg/kg) produced a small reduction in striatal pTA (to 86% of controls) and marked increases in mTA (to 1433% of controls) (table 3). When mice were pretreated with FMD (50 mg/kg) and *m*-tyrosine (2 mg/kg), the levels of pTA were significantly lower than controls while mTA was significantly higher than the controls and about 4 times higher than those treated with *m*-tyrosine alone (table 3).

Discussion

The results confirm that *m*-tyrosine is readily decarboxylated and that *p*-tyrosine, although a much poorer substrate, is also decarboxylated[8]. We presume, because of the reduction in the amount of pTA formed when *m*-tyrosine is present in excess, that this is a consequence of competition either for the enzyme, transfer across the blood brain barrier, or both; a similar effect on mTA formation was noticed when *p*-tyrosine was present in large excess. L-Phenylalanine is clearly a precursor for both mTA and pTA and so we must conclude that it is monohydroxylated, presumably by tyrosine hydroxylase to *m*-or *p*-tyrosine followed by decarboxylation[59]. Initial attempts to identify *m*-tyrosine as a tissue constitutent have not yet been successful (D. A. Durden, personal communication) and we assume that this is because it is metabolized very quickly and thus present in very low concentrations.

Striatal pTA concentrations were reduced after inhibition of central decarboxylase with FMD in doses ranging from 1 to 100 mg/kg (table 2). The treatment, however, increased striatal mTA and was most effective with intermediate doses of FMD (10 mg/kg) while higher doses (50-100 mg/kg) produced lesser increases in mTA (table 2). Also, FMD, increased the formation of mTA from exogenously administered *m*-tyrosine (table 3). Similar findings were obtained after administration of NSD 1055[59]. These results could be explained as the result of a decarboxylase activation produced by the lower doses of FMD or NSD 1055 while the higher doses led to an inhibition of the enzyme.

An explanation of the reciprocal relationship between pTA and DA and mTA can be given most simply on the basis of substrate availability for the decarboxylase enzyme[58]. In the presence of neuroleptic drugs, lesions, γ-hydroxybutyrate, etc.[52,54,56,60], tyrosine hydroxylase is stimulated and thus DOPA and DA are increased. There is consequently a reduction in the amount of *p*-tyrosine available for decarboxylation to pTA. Since *meta*-hydroxylation would be occurring simultaneously with dopamine formation, (i.e. PA, → mTA → DOPA and *p*-tyrosine → DOPA) mTA would be formed by decarboxylation of the *m*-tyrosine[41], a quick reaction utilizing the amino acid as it is produced en route to DOPA. When tyrosine hydroxylase activity is reduced, more *p*-tyrosine becomes available and so pTA increases. We now feel, therefore, that mTA is formed primarily by PA → *m*-tyrosine → mTA and, pTA is formed by *p*-tyrosine → pTA but that this is a slow reaction and affected by the activity of tyrosine hydroxylase. Since pTA also is formed via hydroxylation and dehydroxylation mechanisms, these could be significant in certain metabolic situations and/or certain anatomical or subcellular locations.

The TA's now seem to be very closely related to the synthesis of the catecholamines and because both mTA and pTA enormously potentiate the inhibitory response of neurones to DA and noradrenaline[49], it has been proposed that they exert a neuromodulatory role even though it remains quite possible that either or both the TA's may also be neurotranmitters in their

own right, especially since certain lesions in the mesencephalon have been found to increase mTA content in the caudate[60].

If the tyramines (and some of the other trace amines) are required for normal synaptic functioning in monoaminergic systems as has been proposed[10–12], it is not difficult to envisage how too much or too little of them (i.e. a perturbation in monoaminergic neuronal homeostasis) could be related to the behavioral abnormalities seen in various of the psychiatric disorders.

For the future it remains for us to establish the magnitude and location of the various synthetic tyraminergic pathways, whether the tyramines are neuromodulators, neurotransmitters or both, how and where they function, and how and in which components of behavior they are involved.

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