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DRUG-INDUCED CHANGES IN THE FORMATION, STORAGE AND METABOLISM OF TYRAMINE IN THE MOUSE

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1 The endogenous concentrations of *p*- and *m*-tyramine in the mouse striatum were determined by a mass spectrometric integrated ion current technique and concentrations were 21.3 and 6.1 ng/g, respectively.

2 The present results further confirm that the administration of antipsychotic drugs (chlorpromazine, haloperidol, spiroperidol, α-flupenthixol and (+)-butaclamol) reduces *p*-tyramine concentrations in the mouse striatum. In contrast, striatal *m*-tyramine showed a tendency to increase, although only in the cases of haloperidol and (+)-butaclamol were the differences statistically significant.

3 Administration of antipsychotic drugs to mice pretreated with tranylcypromine or clorgyline produced a significant reduction in striatal *p*-tyramine when compared with the concentrations obtained in mice given a monoamine oxidase inhibitor. These results suggest that antipsychotic drugs reduce striatal *p*-tyramine formation. The moderate increases produced by monoamine oxidase inhibitors on striatal *m*-tyramine were not significantly changed after the administration of an antipsychotic.

4 Drugs that reduce dopamine turnover (apomorphine, piribedil, lergotrile, α-methyl-*p*-tyrosine) significantly increased the concentration of striatal *p*-tyramine. No significant changes were observed in striatal *m*-tyramine concentrations after apomorphine, piribedil or lergotrile; α-methyl-*p*-tyrosine produced a reduction in its concentration.

5 Drugs that impair amine storage (reserpine, tetrabenazine, oxypertine) reduced striatal concentrations of *p*-tyramine. The *m*-tyramine concentrations were also reduced by reserpine or tetrabenazine.

6 It is possible that striatal tyramines act as modulators, or transmitters, and control the activity of dopaminergic neurones.

Introduction

The administration of clinically active antipsychotic drugs blocks the dopamine postsynaptic receptor sites and increases the rate of dopamine turnover (Carlsson & Lindquist, 1963; Andén, Roos & Werdinius, 1964; Laverty & Sharman, 1965; O'Keeffe, Sharman & Vogt, 1970). More recent work has shown that the administration of antipsychotic drugs also produces a substantial reduction (to 25 to 43% of controls) in mouse striatal *p*-tyramine levels (Juorio, 1977a) and a similar reduction has also been observed in the rat striatum (Juorio & Danielson, 1978).

In an attempt to elucidate whether this effect was a consequence of an increase in *p*-tyramine metabolism or a reduction in its formation, the effect of the administration of antipsychotic drugs on the striatal *p*-tyramine concentration was examined after blockade of its metabolism by administration of monoamine oxidase inhibitors. Since the changes induced by antipsychotic drugs in striatal *p*-tyramine may be related to the increase in dopamine turnover they produce, it was decided to study the effect on striatal *p*-tyramine levels of drugs that reduce dopamine turnover by receptor activation or synthesis blockade. The effects of drugs that interfere with amine storage (reserpine and related compounds) were also studied. For comparison, the striatal levels of *m*-tyramine and sometimes those of dihydroxyphenylacetic acid were also examined.

Methods

Male albino Swiss mice (18 to 22 g body weight) were killed by decapitation. The brain was removed and the striatum, consisting mainly of the head of the caudate nucleus and including some of the underlying putamen (approximate weight 28 to 35 mg per animal), was dissected out. Striata from three animals

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were pooled, immediately frozen in dry ice, weighed and homogenized in 0.1 N HCl containing disodium edetate (EDTA, 1 mg/ml) and ascorbic acid (5 mg/ml). The amines in the tissue homogenate were derivatized with 5-dimethylamino-1-napthalenesulphonyl (dansyl) chloride and the resultant derivatives extracted in benzene, evaporated to a small volume, separated chromatographically and estimated by the high resolution mass spectrometric integrated ion current technique using deuterated *p*- or *m*-tyramine as internal standards. This procedure has been described in detail (Philips, Durden & Boulton, 1974a; Philips, Davis, Durden & Boulton, 1975). Dihydroxyphenylacetic acid (DOPAC) was estimated by a fluorimetric method, tissue homogenates were acidified, extracted with ethylacetate, condensed with ethylene diamine and the fluorescence measured (Murphy, Robinson & Sharman, 1969); results were corrected for 83 ± 5% recovery (mean ± s.e. mean, calculated from 5 experiments). Drugs were dissolved in 0.9% w/v NaCl solution (saline) and injected intraperitoneally. Haloperidol, spiperone, piribedil, oxypertine, reserpine and lergotrile mesylate were dissolved in 50 to 100 µl of glacial acetic acid. The first three of these drugs were then diluted 40 to 50 times with saline, the others with isotonic glucose solution. (+)-Butaclamol hydrochloride and (−)-butaclamol hydrochloride were suspended in saline containing 2.2 mg/ml of Tween 80. Controls were injected with the corresponding vehicle solution. The drugs were generously provided as follows: tranylcypromine sulphate and chlorpromazine hydrochloride, Smith, Kline & French Laboratories, Philadelphia, Pennsylvania, U.S.A.; clorgyline hydrochloride, May & Baker Ltd.; haloperidol and spiperone, Janssen Pharmaceutica, Beerse, Belgium; α-flupenthixol dihydrochloride and β-flupenthixol dihydrochloride, H. Lundbeck & Co., Copenhagen, Denmark; (+)-butaclamol hydrochloride and (−)-butaclamol hydrochloride, Ayerst Laboratories, Montreal, Canada; piribedil, Les Laboratoires Servier, Orléans, France; lergotrile mesylate, Eli Lilly & Co., Indianapolis, Indiana, U.S.A.; oxypertine, Sterling–Winthrop Research Institute, Renssalaer, New York, U.S.A.; tetrabenazine methane sulphonate, Hoffman–La Roche, Inc., Nutley, New Jersey, U.S.A. The following drugs were obtained from commercial sources: DL-α-methyl-*p*-tyrosine methyl ester, reserpine and apomorphine hydrochloride.

Results

Effect of tranylcypromine, clorgyline and some antipsychotic drugs on striatal tyramines

The intraperitoneal administration of tranylcypromine (2 mg/kg) and clorgyline (10 mg/kg) increased significantly the concentrations of *p*-tyramine to 2.5 and 4 times, respectively, those observed in control animals (Table 1); the effects on *m*-tyramine concentrations were less marked with increases of only 1.4 to 1.7 times the control value being observed

Table 1 Effects of the intraperitoneal administration of chlorpromazine or (+)-butaclamol and some amine oxidase inhibitors on mouse striatal *p*-tyramine and *m*-tyramine

Treatment	*Dose (mg/kg)*	*Time (h)*	p-*Tyramine (ng/g)*	m-*Tyramine (ng/g)*
Controls	—	—	21.8 ± 1.2 (40)	6.2 ± 0.3 (36)
Tranylcypromine	2	2.5	54.4 ± 6.3 (7)***	9.9 ± 1.2 (5)**
Chlorpromazine	20	2	5.3 ± 0.7 (4)***	7.8 ± 1.9 (4)
Tranylcypromine +	2	2.5	T**	
chlorpromazine	20	2	20.7 ± 4.0 (4)	11.9, 6.6 (2)
(+)-Butaclamol	1	2	6.6 ± 0.8 (6)***	10.4 ± 2.0 (6)*
Tranylcypromine +	2	2.5	T*	
(+)-butaclamol	1	2	27.9 ± 4.5 (3)	11.7 ± 1.4 (3)***
Clorgyline	10	2.5	88.4 ± 6.3 (20)***	10.4 ± 0.6 (20)***
Chlorpromazine	2	2	7.6 ± 0.7 (6)***	7.2 ± 0.9 (6)
Clorgyline +	10	2.5	Cl***	
chlorpromazine	2	2	49.5 ± 2.7 (9)***	8.6 ± 0.9 (9)*
Clorgyline +	10	2.5	Cl***	Cl***
chlorpromazine	20	2	39.3 ± 4.9 (5)***	6.2 ± 0.9 (5)

The mice were treated with clorgyline or tranylcypromine and 0.5 h later given chlorpromazine; the animals were killed 2.5 h after the beginning of the experiment. Values are means ± s.e. mean, (number of experiments in parentheses) in ng/g of fresh tissue. Student's *t* test: * $P < 0.01$, ** $P < 0.005$, *** $P < 0.001$; Cl or T indicate that the *t* values were obtained by comparison with animals treated with clorgyline or tranylcypromine, respectively.

(Table 1). Clinically active antipsychotic drugs (chlorpromazine, α-flupenthixol, haloperidol, spiperone, (+)-butaclamol) produced a marked and statistically significant reduction (to 24 to 35% of controls) in mouse striatal *p*-tyramine (Tables 1 and 2). The *m*-tyramine concentrations were somewhat increased but only in the cases of haloperidol and (+)-butaclamol did the increase reach statistical significance (Tables 1 and 2). Chemically related compounds (β-flupenthixol, (−)-butaclamol) lacking antipsychotic activity did not produce any statistically significant changes in mouse striatal *p*- or *m*-tyramine levels (Table 2). The administration of tranylcypromine (2 mg/kg) or clorgyline (10 mg/kg), 2.5 h before death, in association with chlorpromazine (2 or 20 mg/kg), 2 h before death, resulted in a reduction in *p*-tyramine concentrations to about 38 to 56% compared with the concentrations found after tranylcypromine or clorgyline alone (Table 1). Similar reductions (36 to 50%) were observed for animals pretreated with clorgyline (10 mg/kg) in association with α-flupenthixol (2 mg/kg), haloperidol (0.2 mg/kg), spiperone (0.2 mg/kg) or (+)-butaclamol (1 mg/kg); the reductions obtained were in all cases statistically significantly different from the values obtained after the administration of clorgyline alone, as well as from the control values (see Table 2). β-Flupenthixol or (−)-butaclamol, drugs that lack antipsychotic activity, did not change the striatal *p*-tyramine concentrations observed in clorgyline-treated mice (Table 2). The clorgyline-induced increases in striatal *m*-tyramine were not changed after administration of chlorpromazine, α- or β-flupenthixol, spiperone or (−)-butaclamol (Tables 1 and 2); a small reduction was observed with haloperidol and a small increase with the non-antipsychotic compound, (−)-butaclamol (Table 2).

Effects of administration of apomorphine, piribedil or lergotrile on striatal tyramine and dihydroxyphenylacetic acid levels

The intraperitoneal administration of apomorphine (20 mg/kg) produced a marked increase in the concentration of striatal *p*-tyramine (Table 3). The maximal effect (an increase to about 166% of the control values) was observed about 1 h after drug administration; values had returned to their control levels after 2 h (Table 3). No significant changes were observed for *m*-tyramine (Table 3). Treatment with piribedil (1 or 10 mg/kg) produced statistically significant in-

Table 2 Effects of the intraperitoneal administration of some antipsychotic drugs, related compounds and clorgyline on mouse striatal *p*-tyramine and *m*-tyramine

Treatment	*Dose (mg/kg)*	*Time (h)*	p-*Tyramine (ng/g)*	m-*Tyramine (ng/g)*
Controls	—	—	21.8 ± 1.2 (40)	6.2 ± 0.3 (36)
Clorgyline	10	2.5	88.4 ± 6.3 (20)***	10.4 ± 0.6 (20)***
α-Flupenthixol	2	2	5.5 ± 0.6 (9)***	6.9 ± 1.0 (7)
Clorgyline +	10	2.5	Cl***	
α-flupenthixol	2	2	44.4 ± 6.3 (5)**	8.1 ± 1.4 (5)
β-Flupenthixol	2	2	21.0 ± 2.0 (9)	6.2 ± 0.4 (7)
Clorgyline +	10	2.5		
β-Flupenthixol	2	2	87.2 ± 8.0 (4)***	11.7 ± 0.5 (4)***
Haloperidol	0.2	2	7.1 ± 0.4 (3)***	10.0 ± 0.3 (3)***
Clorgyline +	10	2.5	Cl***	Cl*
haloperidol	0.2	2	58.0 ± 1.8 (4)***	8.6 ± 0.2 (4)***
Spiperone	0.2	2	6.0 ± 1.4 (8)***	7.5 ± 0.7 (8)
Clorgyline +	10	2.5	Cl***	
spiperone	0.2	2	42.4 ± 2.4 (5)***	9.4 ± 0.8 (4)***
(+)-Butaclamol	1	2	6.6 ± 0.8 (6)***	10.4 ± 2.0 (6)*
Clorgyline +	10	2.5	Cl***	
(+)-butaclamol	1	2	31.6 ± 2.4 (6)***	10.0 ± 0.7 (5)***
(−)-Butaclamol	1	2	24.3 ± 2.8 (4)	7.2 ± 1.3 (4)
Clorgyline +	10	2.5		Cl*
(−)-butaclamol	1	2	76.5 ± 8.8 (6)***	13.2 ± 1.0 (5)***

The mice were treated with clorgyline and 0.5 h later given the antipsychotic drug; the animals were killed 2.5 h after the beginning of the experiment. Values are means (± s.e. mean, number of experiments in parentheses) in ng/g of fresh tissue. Student's *t* test: * $P < 0.05$; ** $P < 0.005$; *** $P < 0.001$; Cl indicates that the *t* values were obtained by comparison with animals treated with clorgyline.

creases (to 132 and 162% of the controls, respectively) at both dose levels, an effect observed 1 h after drug administration (Table 3). Similar increases (178% of the control values) were observed 1 h after lergotrile administration (10 mg/kg) (Table 3). The values of dihydroxyphenylacetic acid were reduced (to 40 to 50% of controls) after the administration of either apomorphine, piribedil or lergotrile (Table 3).

Effects of administration of α-methyl-p-tyrosine, reserpine, tetrabenazine or oxypertine on striatal tyramines

The subcutaneous administration of α-methyl-*p*-tyrosine methyl ester (200 mg/kg) produced a statistically significant increase (194% of control values) in concentrations of *p*-tyramine. The levels of *m*-tyramine were reduced to 57% of the control values (Table 4). The administration of reserpine (1 mg/kg), tetrabenazine (20 mg/kg) or oxypertine (10 mg/kg) produced marked reductions to 10, 16 or 34% of controls, respectively, in the *p*-tyramine levels (Table 4); *m*-tyramine was reduced to a lesser extent (to 21, 10 or 62% of controls) (Table 4) and in the case of oxypertine, the reduction was not statistically significant.

Discussion

Interest in tyramine is not new; its synthesis was described many years ago (Schmitt & Nasse, 1865; Barger, 1909) as well as its fate after being fed to dogs or perfused through isolated organs such as the liver or the uterus. Both methods resulted in the formation of *p*-hydroxyphenylacetic acid that was detected in urine or the effluent perfusate (Ewins & Laidlaw, 1910). A few years later, this substance was isolated (presumably as the *p*-isomer) from the *Octopus* posterior salivary gland (Henze, 1913). Many essentially pharmacological studies of the effect of *p*-tyramine as releaser of other amines followed (see review by Trendelenburg, 1972) and it was only after the development of a specific and sensitive mass spectrometric technique that the cerebral concentrations of *p*- and *m*-tyramine were measured (Philips *et al.*,

Table 3 Effects of the intraperitoneal administration of apomorphine, piribedil or lergotrile on mouse striatal *p*-tyramine, *m*-tyramine and dihydroxyphenylacetic acid (DOPAC) concentrations

	Dose (*mg/kg*)	*Time* (*h*)	p-*Tyramine* (*ng/g*)	m-*Tyramine* (*ng/g*)	*DOPAC* (*ng/g*)
Controls	—	—	22.9 ± 1.8 (17)	6.2 ± 0.4 (15)	694 ± 53 (9)
Apomorphine	20	0.5	31.7 ± 4.5 (5)	5.8 ± 1.2 (3)	—
Apomorphine	20	1	37.9 ± 2.4 (7)***	5.5 ± 0.7 (5)	301 ± 31 (7)***
Apomorphine	20	2	22.1 ± 0.7 (4)	5.1 ± 0.9 (3)	—
Piribedil	1	1	30.3 ± 2.1 (6)*	6.9 ± 0.6 (6)	—
Piribedil	10	1	37.0 ± 3.6 (8)**	7.3 ± 0.4 (8)	399 ± 43 (5)***
Lergotrile	10	1	40.7 ± 4.3 (6)**	7.6 ± 0.8 (6)	339 ± 36 (5)***

Values are means ±s.e. mean, (number of experiments in parentheses) in ng/g of fresh tissue and corrected for recovery. Student's *t* test: * $P < 0.025$; ** $P < 0.005$; *** $P < 0.001$.

Table 4 Effects of the subcutaneous administration of some drugs on mouse striatal *p*-tyramine and *m*-tyramine levels

	Dose (*mg/g*)	*Time* (*h*)	p-*Tyramine* (*ng/g*)	m-*Tyramine* (*ng/g*)
Controls	—	—	19.3 ± 0.9 (19)	5.8 ± 0.5 (14)
α-Methyl-*p*-tyrosine	200	2	37.4 ± 2.4 (6)**	3.3 ± 0.9 (6)*
Reserpine	1	24	1.9 ± 0.8 (4)**	1.2 ± 0.4 (4)**
Tetrabenazine	20	1	3.1 ± 0.4 (7)*	1.1 ± 0.6 (6)**
Oxypertine	10	2	6.5 ± 1.4 (5)*	3.6 ± 1.0 (5)

Values are means ± s.e. mean, (number of experiments in parentheses) in ng/g of fresh tissue. Student's *t* test: * $P < 0.01$; ** $P < 0.001$.

1974a; Philips *et al.*, 1975). Brain tyramine concentrations (of the *p*- and *m*-isomers together) were also determined by a radioenzymatic method (Tallman, Saavedra & Axelrod, 1976a); their values are of the same order though somewhat higher than those obtained mass spectrometrically (Philips *et al.*, 1974a; Philips, *et al.*, 1975). The highest concentration of brain *p*- and *m*-tyramine (11 to 3 ng/g, respectively) were found in the striatum (Boulton, 1976) where they appear to be stored by a reserpine-sensitive mechanism (Boulton, Juorio, Philips & Wu, 1977). The administration of pargyline produced a marked accumulation (over 1500-fold) of intraventricularly administered radiolabelled *p*-tyramine (Wu & Boulton, 1974) as well as marked increases (8- to 10-fold) in the endogenous brain levels of both *p*- and *m*-tyramine (Boulton, Juorio, Philips & Wu, 1975) thus suggesting that these amines possess a high metabolic rate and are inactivated by a monoamine oxidase enzyme. This is further supported by the finding that the ratio of the concentration of the acid metabolite to that of its respective amine in the case of *p*-tyramine as well as of other trace amines such as β-phenylethylamine or tryptamine is far greater (range 13 to 153) than the ratio obtained for dopamine or 5-hydroxytryptamine (0.4 to 0.6) (Table 5) and may suggest that the tyramines have a role in brain function and are not merely metabolic accidents (Boulton, 1974; 1978; Baldessarini & Fisher, 1978).

The use of different monoamine oxidase inhibitors and substrates suggests that monoamine oxidase may exist in two forms which have been designated type A and type B; clorgyline appears to be a specific type A monoamine oxidase inhibitor (Johnston, 1968) whereas tranylcypromine inhibits both the type A and the type B enzyme (Neff & Yang, 1974); tyramine (presumably *para*) is a good substrate for both types of enzyme (Neff & Yang, 1974). In this series of experiments, both tranylcypromine or clorgyline produced substantial increases (2 to 4 times) in striatal *p*-tyramine levels. The comparatively smaller increases produced by clorgyline or tranylcypromine on striatal *m*-tyramine (0.6 to 0.7 times) suggest that this amine is not as good a substrate for monoamine oxidase as is *p*-tyramine; alternatively, it may indicate that *m*-tyramine possesses a lower synthesis rate. In addition, these increases are similar to those exhibited by the catecholamines (Green & Erickson, 1960; Yang & Neff, 1974) and in this respect, it is interesting to note that *m*-tyramine seems to be derived predominantly by dehydroxylation of DOPA or dopamine (Boulton & Dyck, 1974).

Antipsychotic drugs (chlorpromazine, haloperidol, α-flupenthixol and (+)-butaclamol) produce significant decreases, in striatal *p*-tyramine (Juorio, 1977a) and this effect has now been further confirmed and extended to spiperone. Furthermore, the administration of antipsychotic drugs to animals pretreated with a monoamine oxidase inhibitor produced marked reductions in striatal *p*-tyramine levels when compared with those obtained in mice pretreated with only the monoamine oxidase inhibitor. No such changes were produced by structurally related compounds devoid of antispychotic properties. These findings strongly suggest that antispychotic drugs reduce the formation of *p*-tyramine in the striatum.

Table 5 The acid metabolite:amine ratio for some trace amines and classical transmitters

Compound	*Concentration (ng/g)*	*Ratio*
p-Hydroxyphenylacetic acid	26[1]	13
p-Tyramine	2.0[2]	
Phenylacetic acid	275[3]	153
β-Phenylethylamine	1.8[4]	
Indolyl-3-acetic acid	12[5]	24
Tryptamine	0.5[6]	
Dihydroxyphenylacetic acid + homovanillic acid	1900[7] + 480[7]	0.4
Dopamine	5530[7]	
5-Hydroxyindolylacetic acid	370[8]	0.6
5-Hydroxytryptamine	620[8]	

Concentration of amines and metabolites are for the rat whole brain, except for dopamine and acid metabolites that are striatal values.

The superscript indicates the source of the reference: (1) Karoum, Gillin & Wyatt (1975); (2) Philips, Durden & Boulton (1974a); (3) Madubuike & Mosnaim (1975); (4) Durden, Philips & Boulton (1973); (5) Warsh, Chan, Godse, Coscina & Stancer (1977); (6) Philips, Durden & Boulton (1974b); (7) Guldberg & Broch (1971); (8) Robinson & Sharman (1967).

In the case of *m*-tyramine, no reduction was observed in its formation; it has to be considered, however, that the monoamine oxidase inhibitors employed produced only a limited increase in striatal *m*-tyramine. Since the increase in dopamine turnover induced by the antipsychotic drugs is accompanied by a reduction in the formation of *p*-tyramine, it was suggested that drugs that reduce dopamine turnover would cause an increase in *p*-tyramine concentration. The compounds chosen were some dopamine receptor agonists (apomorphine, piribedil or lergotrile) and an inhibitor of dopamine synthesis (α-methyl-*p*-tyrosine). Activation of the dopamine–receptor sites induced by apomorphine, piribedil and lergotrile produced a reduction in the turnover of striatal dopamine as demonstrated by reduction in the concentration of their acid metabolites (Roos, 1969; Corrodi, Fuxe & Ungerstedt, 1971; Fuller & Perry, 1978). In the present series of experiments, these findings have been further confirmed as shown by the reduction observed in the striatal levels of dihydroxyphenylacetic acid. As anticipated, the three dopamine–receptor agonists produced a marked increase in the striatal level of *p*-tyramine.

Inhibition of dopamine synthesis caused by α-methyl-*p*-tyrosine (Spector, Sjoerdsma & Udenfriend, 1965) was followed by a reduction in the striatal concentrations of dihydroxyphenylacetic acid (A.V. Juorio, unpublished observation) and a marked increase in striatal *p*-tyramine levels. This could be the result of an increased availability of *p*-tyrosine that is decarboxylated to *p*-tyramine. However, the affinity of this amino acid for the decarboxylase is lower than that of DOPA, tryptophan or phenylalanine (Christenson, Dairman & Udenfriend, 1970). Dehydroxylation of dopamine has been postulated as one of the pathways for the synthesis of *m*-tyramine (Boulton & Dyck, 1974) and the reduction in striatal *m*-tyramine levels observed after α-methyl-*p*-tyrosine would certainly agree with this suggestion. It was recently reported that the administration of α-methyl-*p*-tyrosine produced no significant changes in brain tyramine levels (Tallman *et al.*, 1976b). Since the treatment changed the levels of *p*- and *m*-tyramine in opposite directions (Table 4) and the radiochemical method used by these authors does not resolve the *p*- and *m*-isomers of tyramine, this would, at least, partly explain the difference.

Reserpine impairs the storage of neural catecholamines and causes a reduction in its concentration (Holzbauer & Vogt, 1956; Bertler, 1961) and similar reductions have recently been observed for the rat striatal *p*- and *m*-tyramine (Boulton *et al.*, 1977); mouse striatal tyramine levels are also reduced by reserpine. In addition, the administration of tetrabenazine or oxypertine, substances that are known to interfere with amine storage (Pletscher, Besendorf & Bächtold, 1958; Fuxe, Grobecker, Hökfelt, Johnsson & Malmfors, 1967; O'Keeffe *et al.*, 1970) have been shown to reduce the mouse striatal levels of both tyramine isomers. Interestingly, in some recent *in vitro* studies (Lentzen & Philippu, 1977) it has been shown that tyramine is taken up by isolated striatal synaptic vesicles by an ATP-Mg^{2+}-dependent process that is inhibited by reserpine.

An intriguing finding is that administration of (+)-amphetamine to mice pretreated with either chlorpromazine or haloperidol caused a further decrease in the striatal *p*-tyramine levels that was significantly different from that produced by the antipsychotics alone; the moderate increase in *m*-tyramine produced by chlorpromazine, haloperidol or (+)-amphetamine, respectively, was also markedly potentiated when (+)-amphetamine was given to chlorpromazine or haloperidol-treated mice (Juorio, 1977b) and similar results were observed for the rat (Juorio & Danielson, 1978). These findings have been related to the dopamine-releasing effect of (+)-amphetamine (Juorio, 1977b) or may be due to changes in dopamine receptor sensitivity induced by (+)-amphetamine (Jenner, Pycock & Marsden, 1978) and provide another example of the complexity of interrelationships of brain amines.

The regulation of most physiological functions is achieved as a consequence of a balance between two or more transmitter systems, such as occurs in the autonomic nervous system (see discussion by Davis, 1975). The present experiments show that an increase in striatal dopamine turnover induced by the administration of antipsychotic drugs is accompanied by a decrease in the concentration and synthesis of striatal *p*-tyramine. Conversely, decreases in striatal dopamine turnover as caused by dopamine-receptor agonists or enzyme inhibitors of dopamine synthesis, increases the concentration of striatal *p*-tyramine. The levels of striatal *m*-tyramine did not appear to be affected by the dopamine receptor agonists; and inhibition of dopamine synthesis (by α-methyl-*p*-tyrosine) produced a reduction in *m*-tyramine levels. These findings suggest that the physiological function of striatal *p*-tyramine may be to act as a modulator or a transmitter, perhaps by forming part of a regulatory loop that controls the functional activity of dopaminergic terminals.

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