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EFFECTS OF MOLINDONE AND FLUPHENAZINE ON THE BRAIN CONCENTRATION OF SOME PHENOLIC AND CATECHOLIC AMINES IN THE MOUSE AND THE RAT

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1 The concentrations of *p*- and *m*-tyramine, dopamine, 3,4-dihydroxyphenylacetic acid and homovanillic acid were measured in the mouse or rat striatum following the subcutaneous injection of molindone or fluphenazine. The mouse hypothalamic levels of the *m*- or *p*-isomers of octopamine were also analysed.

2 Endogenous concentrations of *p*- and *m*-tyramine in the mouse striatum and *p*- and *m*-octopamine in the mouse hypothalamus were 20.6, 5.7, 9.4 and 1.2 ng/g respectively. The rat striatum concentrations of *p*- and *m*-tyramine were 12.8 and 3.8 ng/g.

3 The administration of low doses of molindone (1 to 10 mg/kg) produced a reduction in striatal *p*-tyramine, an increase in *m*-tyramine and an increase in dopamine turnover. Similar effects were produced by all doses of fluphenazine (0.1 to 5 mg/kg) employed. These findings are consistent with those observed after blockade of dopamine postsynaptic receptors.

4 With high doses of molindone (100 mg/kg) the effects on both tyramines and on dopamine metabolism were reversed. These results can be interpreted as molindone acting as a partial agonist.

5 The concentrations of hypothalamic *p*- and *m*-octopamine were increased by the higher doses of molindone (20 to 100 mg/kg) employed while lower doses produced no significant effects. All doses of fluphenazine reduced hypothalamic *p*-octopamine. These changes seem to depend on differences in the availability of *p*-tyramine to be converted into *p*-octopamine.

6 These results suggest that molindone acts as a blocker or a partial agonist of dopamine receptor sites and fit well with the proposal of a reciprocal relation between dopamine and tyramine. It is not possible yet to ascertain whether tyramine controls dopamine or *vice versa* or if it is a direct or a more remote relation.

Introduction

Molindone (3-ethyl-6, 7-dihydro-2-methyl-5-morpholino methyl indole-4-(5H)-one hydrochloride) is an indole derivative with neuroleptic effects in animals (Rubin, Yen & Pfeffer, 1967) and which in humans possesses an antipsychotic activity equivalent to that observed for the phenothiazines and butyrophenones (Clark, Huber, Sakata, Fowler & Serafetinides, 1970). It possesses the advantage of not antagonizing the antihypertensive effects of guanethidine (Gilder, Fain & Simpson, 1976). Clinically efficacious antipsychotic drugs bind to and block dopamine receptor sites (Seeman, Chau-Wong, Tedesco & Wong, 1975; Burt, Enna, Creese & Snyder, 1975) and increase dopamine turnover rate (Carlsson & Lindquist, 1963; Andén, Roos & Werdinius, 1964; Laverty & Sharman, 1965b; O'Keeffe, Sharman & Vogt, 1970); a similar effect has been observed for molindone (Bunney, Roth & Aghajanian, 1975). The increase in striatal dopamine turnover induced by antipsychotic drugs has been shown to occur in association with a reduction in *p*-tyramine concentration (Juorio, 1977a; Juorio & Danielson, 1978; Juorio, 1979a; Boulton & Juorio, 1979). This reduction in *p*-tyramine may be a consequence of a reduction in its formation (Juorio, 1979a).

In this study I have investigated the effect of molindone on the concentrations of striatal tyramine and dopamine metabolism in the mouse and rat striatum. For comparative purposes simultaneous changes induced by molindone on hypothalamic octopamine and the effects of fluphenazine on some amines and metabolites were also studied.

Methods

Male albino Swiss mice (18 to 22 g body wt.) or male Wistar rats (200 to 240 g body wt.) were killed by decapitation. The brain was removed quickly and the

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striatum, consisting mainly of the head of the caudate nucleus and including some of the underlying putamen (approximate weights 28 to 35 mg for the mice and 100 to 130 mg for the rats) was dissected out. The hypothalamus, found below the thalamus and between the anterior and posterior commissura (approximate weight 9 to 11 mg for the mice) was also removed. Striata from three mice or two rats 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-naphthalene sulphonyl (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. Complete details concerning this procedure have been described (Philips, Durden & Boulton, 1974; Philips, Davis, Durden & Boulton, 1975). The octopamine estimations were carried out on the pooled hypothalami of three mice. Tissue homogenates were prepared in 100 mM Tris buffer in the presence of 1.3 mM pargyline and then heated to denature the proteins which were then removed by centrifugation. Portions of the deproteinized supernatant corresponding to about 10 mg of tissue were then incubated with partially purified phenylethanolamine-*N*-methyltransferase (E.C.2.1.1.) and tritiated *S*-adenosylmethionine which served as a methyl donor substance (Molinoff, Lansberg & Axelrod, 1969; Saavedra, 1974). Internal standards were prepared by adding supplements of *p*- or *m*-octopamine to a portion of each tissue homogenate and the blanks were prepared by the addition of Tris-HCl buffer solution. The *p*-synephrine and *m*-synephrine formed in the reaction were extracted with ethyl acetate, transferred to a different test tube and evaporated to dryness; the residues were dissolved in sodium carbonate solution and 1-dimethylamino-naphthalene-5-sulphonyl (dansyl) chloride (Danielson, Boulton & Robertson, 1977) added; after extraction with benzene the volume was reduced and after transferring to a chromatogram, separated, the zones removed and the amount of radioactivity in them measured. The reagent blanks amounted to 3 to 8 pg for *p*-octopamine and 6 to 11 pg for *m*-octopamine respectively and the minimum detectable was twice as much as in the blanks. Dopamine was estimated by the fluorimetric method proposed by Laverty & Sharman (1965a). The estimations were carried out on the pooled striata of two mice. Dopamine was separated on a Dowex 50W X4 ion exchange chromatography column, acetylated, a fluorophore developed by condensation with 1,2-diaminoethane and the fluorescence products extracted into isobutanol and estimated. Checks on recoveries of 100 ng of added dopamine were carried out in each experiment; the percentage recovery was 75 ± 2 (12) (mean ± s.e. of mean, number of experiments in parentheses). The results were corrected for losses. 3,4-Dihydroxyphenylacetic acid and 4-hydroxy-3-methoxy-phenylacetic acid (homovanillic acid) were estimated in the pooled striata of three or five mice or two rats respectively. The tissues were homogenized in 0.1 N HCl, deproteinized with 0.4 N perchloric acid and extracted with butylacetate. 3,4-Dihydroxyphenylacetic acid was analyzed by a fluorimetric method, essentially as described by Murphy, Robinson & Sharman (1969). Homovanillic was extracted from the butylacetate into 0.05 M Tris buffer and estimated fluorimetrically (Andén, Roos & Werdinius, 1963). Checks on the recoveries of 50 to 200 ng of added acids were carried out in every experiment; the percentage recovery was (means ± s.e. of mean, number of experiments in parentheses) for 3,4-dihydroxyphenylacetic acid 74 ± 4 (11) and for homovanillic acid 81 ± 2 (16). The results were corrected accordingly.

The drugs were dissolved in 0.9% w/v NaCl solution (saline) and injected subcutaneously. Molindone hydrochloride was generously provided by Endo Laboratories, Inc., N.Y., U.S.A. and fluphenazine dihydrochloride by E.R. Squibb & Sons, Inc., N.J., U.S.A.

Results

Two hours after the subcutaneous administration of 0.2 mg/kg molindone, no significant change in the striatal concentration of *p*- or *m*-tyramine (Table 1) or 3,4-dihydroxyphenylacetic acid (Table 2) could be detected. A higher dose of molindone (2 mg/kg) produced at 2 h after drug administration, a significant reduction (to 64% of controls) in striatal *p*-tyramine accompanied by a significant increase (to 181% of controls) in *m*-tyramine and no significant changes in hypothalamic octopamines (Table 1). The concentrations of striatal dopamine were not significantly changed and those of 3,4-dihydroxyphenylacetic acid and homovanillic acid were significantly increased (to about 158 and 233% of controls respectively) (Table 2). By increasing the dose of molindone to 20 mg/kg, the striatal concentrations of both *p*- and *m*-tyramine were increased (to 120–150% of controls) at 1 to 2 h after drug administration (Table 1), hypothalamic *p*-and *m*-octopamine increased even more (to 170 to 290% of controls). The maximum increase in striatal tyramines or hypothalamic octopamines was observed at 4 to 24 h after the drug injection (20 mg/kg) and ranged from 150 to 410% of controls (Table 1). This high dose of molindone produced a short lasting reduction in striatal dopamine (to 74%

Table 1 Effects of the subcutaneous administration of molindone or fluphenazine on mouse cerebral *p*-tyramine (*p*-TA), *m*-tyramine (*m*-TA), *p*-octopamine (*p*-OA) and *m*-octopamine (*m*-OA)

Treatment	*Dose* (*mg/kg*)	*Time* (*h*)	p-*TA* (*ng/g*)	m-*TA* (*ng/g*)	p-*OA* (*ng/g*)	m-*OA* (*ng/g*)
			Striatum		*Hypothalamus*	
Controls			20.6 ± 1.2 (29)	5.7 ± 0.3 (28)	9.4 ± 0.4 (19)	1.2 ± 0.1 (12)
Molindone						
	0.2	2	22.8 ± 1.9 (5)	6.1 ± 0.6 (5)	—	—
	2	2	13.2 ± 1.5 (8)**	10.3 ± 1.5 (8)**	7.7 ± 0.8 (8)	3.4 ± 1.4 (4)
	20	1	25.6 ± 1.0 (5)**	6.8 ± 0.3 (5)*	16.6 ± 3.0 (8)*	2.0 ± 0.2 (6)**
	20	2	23.7 ± 2.2 (9)	8.4 ± 0.7 (9)**	25.6 ± 2.2 (14)***	3.5 ± 0.3 (5)***
	20	4	29.8 ± 4.3 (7)*	14.5 ± 1.3 (7)***	26.7 ± 2.9 (8)***	4.9 ± 0.5 (5)***
	20	6	46.2 ± 6.4 (5)**	16.5 ± 1.2 (5)***	27.9 ± 1.6 (3)***	4.9 ± 0.1 (3)***
	20	24	40.4 ± 2.7 (4)***	8.1 ± 1.4 (4)	22.6 ± 5.4 (5)**	3.5 ± 0.7 (5)**
	20	72	42.5 ± 9.2 (6)*	8.1 ± 1.4 (6)	17.4 ± 3.4 (8)*	1.7 ± 0.2 (8)*
	20	168	22.3 ± 2.6 (3)	8.6 ± 1.7 (3)	7.1 ± 0.5 (3)	0.9 ± 0.2 (3)
	100	2	46.3 ± 2.1 (8)***	3.7 ± 0.5 (6)**	26.4 ± 3.1 (9)***	2.7 ± 0.4 (6)**
Fluphenazine						
	0.1	2	7.4 ± 0.5 (7)***	6.1 ± 1.0 (7)	7.9 ± 0.8 (8)	1.4 ± 0.1 (8)
	1	2	8.0 ± 0.9 (4)***	10.5 ± 0.8 (4)***	5.5 ± 0.7 (4)***	1.1 ± 0.2 (4)
	5	2	5.5 ± 0.5 (4)***	11.9 ± 0.8 (4)***	3.9 ± 0.5 (4)***	1.5 ± 0.6 (4)

Values are means (±s.e. mean, number of experiments in parentheses) in ng/g of fresh tissue. Student's *t* test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

of controls); the effect was observed at 1 h after the drug injection but returned towards normal at 2 and 4 h (Table 2). The concentrations of 3,4-dihydroxyphenylacetic acid observed 2 h after the administration of 20 mg/kg of molindone were similar to the controls but statistically significantly lower than those concentrations obtained after the administration of 2 mg/kg (Table 2), and in the case of homovanillic acid the concentrations after 20 mg/kg were statistically significantly higher than the controls, but lower than after 2 mg/kg (Table 2). The maximum increase in striatal tyramine and hypothalamic octopamine was observed 6 h after the administration of 20 mg/kg of molindone (Table 1). Increases in both *p*-tyramine

Table 2 Effects of the subcutaneous administration of molindone or fluphenazine on mouse striatal dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and 4-hydroxy-3-methoxyphenylacetic acid (HVA)

	Dose (*mg/kg*)	*Time* (*h*)	*DA* (*ng/g*)	*DOPAC* (*ng/g*)	*HVA* (*ng/g*)
Controls			8440 ± 590 (13)	640 ± 50 (18)	920 ± 90 (7)
Molindone					
	0.2	2	—	750 ± 190 (4)	—
	2	2	7880 ± 1020 (6)	1010 ± 120 (6)**	2140 ± 150 (7)***
	20	1	6210 ± 390 (7)**		
	20	2	7550 ± 530 (6)	650 ± 90 (6)†	1510 ± 70 (7)***††
	20	4	7700 ± 470 (5)		
	100	2	7120 ± 540 (8)	420 ± 60 (6)*†††	1300 ± 90 (7)*††††
Fluphenazine					
	0.1	2	6100 ± 360 (6)**	2300 ± 150 (6)***	2460 ± 170 (6)***
	1	2	—	—	3280 ± 160 (6)***
	5	2	—	—	4070 ± 200 (6)***

Values are means (± s.e. of mean, number of experiments in parentheses) in ng/g of fresh tissue. Student's *t* test * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. † $P < 0.05$, †† $P < 0.005$ or ††† $P < 0.001$ when compared with the group injected with 2 mg/kg of molindone.

and *p*- and *m*-octopamine were observed also at one and three days after drug injection (Table 1). By seven days after molindone administration, the concentrations of both tyramine and octopamine isomers had returned to concentrations that were statistically not different from controls (Table 1). The highest dose of molindone used (100 mg/kg) produced at 2 h after drug administration statistically significant increases in striatal *p*-tyramine and hypothalamic *p*- and *m*-octopamine (to 230 to 280% of controls); in contrast, striatal *m*-tyramine concentrations were not changed (Table 1). This high dose of molindone did not produce any change in the concentration of mouse striatal dopamine but it reduced (to about 65% of controls) that of 3,4-dihydroxyphenylacetic acid (Table 2). The concentrations of homovanillic acid were higher for the controls (141% of controls) but lower than after 2 mg/kg (Table 2). This dose of molindone (100 mg/kg) produced a reduction in mice locomotor activity and skeletal muscle tone. With smaller doses (20 mg/kg) these effects were moderate and not observed in all the animals, and with 0.2 to 2 mg/kg no changes were observed.

Subcutaneous administration of fluphenazine (0.1 mg/kg) produced, at 2 h after drug administration, a reduction in striatal *p*-tyramine (to 36% of controls) but no changes were observed in striatal *m*-tyramine or both isomers of octopamine (Table 1). With higher doses (1 to 5 mg/kg), the reductions in striatal *p*-tyramine were maintained (to 27 to 39% of controls) but *m*-tyramine concentrations were increased (to 180 to 210% of controls) and hypothalamic *p*-octopamine reduced (to 40 to 60% of controls) (Table 1). No changes were observed in hypothalamic *m*-octopamine (Table 1). The fluphenazine treatment produced a significant reduction in the concentration of striatal dopamine (to about 72% of controls), a significant increase in 3,4-dihydroxyphenylacetic acid (to about 360% of controls) and a dose-dependent increase in the concentration of striatal homovanillic acid (Table 2).

In the rat the administration of 1 to 10 mg/kg of molindone produced a significant reduction in striatal *p*-tyramine; with 1 mg/kg the effect was observed 30 min after drug injection and the levels had recovered after 2 h (Table 3) while 10 mg/kg produced a statistically significant decrease that was observed at both 30 min and 2 h (Table 3). These doses of molindone (1 or 10 mg/kg) produced no changes in rat striatal *m*-tyramine (Table 3) and an increase in homovanillic acid (300 to 550% of controls) (Table 3). The higher dose of molindone employed (100 mg/kg) produced an initial reduction in rat striatal *p*-tyramine (to 47% of controls) that was observed 30 min after drug injection (Table 3) and an increase (to 170% of controls) detected at 2 h (Table 3); at this time, the *m*-tyramine concentrations were also increased (to about 160% of controls) (Table 3). With the high dose of molindone (100 mg/kg) the homovanillic acid concentrations were increased with respect to controls (to 240 to 260%); however, the increase was significantly lower than that observed at 2 h after the administration of 10 mg/kg (Table 3).

Discussion

Investigation of the effects of molindone on the mouse or rat striatal tyramine levels and dopamine metabolism has disclosed the existence of two dose-dependent effects. Low doses (1 to 10 mg/kg) produced a reduction in striatal *p*-tyramine, an increase in *m*-tyramine and an increase in the turnover of dopamine as shown by the increases produced in the levels of its acid metabolites (Figure 1 and Table 3). Similar increases in the rat striatum dopamine turnover has been shown by other researchers (Bunney *et al.*, 1975). The effects were similar both in direction

Table 3 Effects of the subcutaneous administration of molindone on rat striatal *p*-tyramine, (*p*-TA), *m*-tyramine (*m*-TA) and homovanillic acid (HVA)

Dose (*mg/kg*)	*Time* (*h*)	p-*TA* (*ng/g*)	m-*TA* (*ng/g*)	*HVA* (*ng/g*)
—	—	12.8 ± 0.2 (7)	3.8 ± 0.5 (7)	730 ± 80 (9)
1	0.5	4.7 ± 1.0 (3)**	2.9 ± 0.3 (3)	2180 ± 190 (5)**
1	2	10.4 ± 1.8 (4)	4.5 ± 0.3 (4)	3070 ± 310 (4)**
10	0.5	3.9 ± 0.4 (4)**	3.1 ± 0.4 (4)	2270 ± 310 (4)**
10	2	4.4 ± 1.0 (4)**	5.1 ± 0.4 (4)	3980 ± 350 (4)**
100	0.5	6.0 ± 0.5 (6)**	3.9 ± 0.6 (6)	1890 ± 250 (5)*
100	2	21.7 ± 2.8 (7)*	6.1 ± 0.4 (7)*	1780 ± 190 (5)*a,b

Values are means (± s.e. of mean, number of experiments in parentheses) in mg/g of fresh tissue. Student's *t* test = * $P < 0.01$, ** $P < 0.001$, (a) compared with the group treated with molindone 10 mg/kg, 2 h $P < 0.001$; (b) compared with the group treated with molindone 1 mg/kg, 2 h $P < 0.01$.

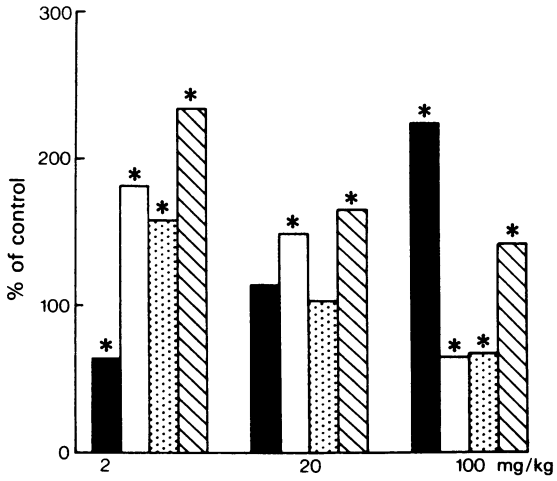

Figure 1 Dose course of the effect of molindone on mouse striatal tyramine, 3,4-dihydroxyphenylacetic acid and homovanillic acid. The abscissae give doses in mg/kg and the ordinates amines or metabolites levels as percentages of controls. The mice were killed 2 h after subcutaneous administration of the drug. Solid columns = *p*-tyramine; open columns = *m*-tyramine; stippled columns = 3,4-dihydroxyphenylacetic acid; hatched columns = homovanillic acid. The asterisks (*) indicate that values are significantly different from controls. Results were summarized from Tables 1 and 2.

and intensity to those produced by all the doses of fluphenazine employed (0.1 to 5 mg/kg) and by injections of chlorpromazine (1 to 100 mg/kg) or haloperidol (0.01 to 10 mg/kg) (O'Keeffe, *et al.*, 1970). These effects with dopamine and its acid metabolites are consistent with the proposal that dopamine postsynaptic receptors are being blocked by molindone.

At high doses of molindone (100 mg/kg) the effects on both tyramines and on dopamine metabolism were reversed; *p*-tyramine was increased, *m*-tyramine was reduced and the concentration of the acid metabolites of dopamine were also reduced (Figure 1 and Table 3). All these changes were significantly different from those observed with the lower dose of the drug (Tables 1, 2 and 3). These effects can be interpreted as the result of molindone acting as a partial agonist on the dopamine presynaptic receptors. Apomorphine and other related dopamine receptor agonists produced similar effects to those obtained after the administration of high doses of molindone (Roos, 1969; Juorio, 1979a).

Blockade of dopamine postsynaptic receptors leads to changes in the affinity of tyrosine hydroxylase for substrate, co-factor or end-product inhibitor that result in an increase in its activity and in the synthesis of dopamine; conversely, activation of dopamine receptors produced a reduction in dopamine synthesis. These effects could be mediated by a presynaptic dopamine receptor located in the nigro-striatal dopamine neurone (see reviews by Walters & Roth, 1974; Carlsson, 1975).

The hypothalamus contains high dopamine-β-hydroxylase activity (Reis & Molinoff, 1972) and is capable of converting *p*-tyramine or *m*-tyramine into their respective β-hydroxylated derivatives (Brandau & Axelrod, 1972). The administration of molindone produces significant increases in the hypothalamic concentration of both *p*- and *m*-octopamine (Table 1). These increases were observed with the higher doses employed (20 to 100 mg/kg), while lower doses produced no detectable effects (Table 1). Since molindone does not inhibit *in vitro* monoamine oxidase (Rubin *et al.*, 1967; P. H. Yu, personal communication) or activate *in vitro* dopamine-β-hydroxylase (P. H. Yu, personal communication) the increases in hypothalamic octopamine would suggest that their respective tyramine precursors are more readily available; the reduction in hypothalamic *p*-octopamine produced by all doses of fluphenazine (0.1 to 5 mg/kg) could be explained as a consequence of decreased availability of *p*-tyramine. In contrast, no significant changes were observed in hypothalamic *m*-octopamine, though the striatal *m*-tyramine concentration was about doubled by the fluphenazine treatment.

These doses of molindone that produced an increase in dopamine turnover, also caused a reduction in *p*-tyramine concentrations and did not change or increase those of *m*-tyramine; these effects are similar to those observed after the administration of antipsychotic drugs, (+)-amphetamine, L-DOPA or the induction of aggregation stress (Juorio, 1977a, b; 1979a, b). Conversely, doses of molindone that decreased dopamine turnover produced an increase in *p*-tyramine concentrations and did not change or reduce those of *m*-tyramine, these effects are similar to those produced by apomorphine or other dopamine receptor agonists or a dopamine synthesis inhibitor (Juorio, 1979a).

These results suggest that molindone acts as a blocker or a partial agonist of dopamine receptor sites and fit well with the proposal of a reciprocal relation between dopamine and tyramine (Juorio, 1979a). It is not possible yet to ascertain whether tyramine controls dopamine or *vice versa*, or if this is a direct or a more complex interrelation.

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